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INFECTION WITH THE VIRUS OF HERPES SIMPLEX*

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PHILADELPHIA

THE virus of herpes simplex, which is primarily a parasite of man, by a process of adaptation through the ages has achieved an enviable relation with its host so that in most cases the two live together almost in a state of symbiosis. However, clinicians are concerned with the relatively uncommon situations in which this ideal arrangement fails and the host responds to the entrance of the parasite with an illness that is sometimes violent.

In the course of the last fifteen years, a good deal of information on the host-parasite relation of this virus (Table 1) has been gathered. In most cases when a susceptible host is exposed to the virus the only evidence of the infection is the development of antibodies. However, when illness results, there are usually two components, a generalized systemic illness that may be severe and sometimes fatal, and a localized reaction that, on the skin and mucous membranes, takes the form of a vesicular eruption. On recovery the patient continues to carry the virus in a latent state and may act as a source of infection of other susceptible persons. In this state he continues to have antibodies circulating in his blood stream, but if his physiologic environment changes, his latent virus may become active and cause a local outbreak of vesicles, the common recurrent "fever blisters." However, there is rarely any overt systemic reaction, presumably because the circulating antibodies prevent an invasion of the blood stream. Until recently, it was thought that this postinfection relation was established immediately, and it may be in many cases. However, a careful study of a number of children after their first exposure to the virus has revealed that this balance of latent virus and antibody may not be established until after a number of reinfections.[1] In other words, after one infection, the child's antibody titer may drop, only to be recalled by another exposure to the virus. Once the balance has been established, the antibody titer remains at a given level irrespective of the number of recurrent attacks of herpes.[2] This forms the paradox that greatly puzzled the early workers in this disease — namely, that only people who had antibodies against herpes ever had attacks of "fever blisters." It is now known that these do not constitute evidence of a new infection but only manifestations of an imbalance between latent virus and host, and that the primary exposure leads to the development of antibodies as in any other infection.

TABLE 1. *Host-Parasite Relation of Herpes Simplex.*

Susceptible host + virus	= primary infection (no circulating antibodies)
Primary infection	= a) manifest disease = local lesion + systemic illness b) subclinical infection = no visible disease
Recovery	= carrier state (circulating antibodies)
Carrier state	= a) recurrent disease = local lesion usually without systemic illness b) latent infection = no visible illness
Carrier state → virus → infection of susceptible host	

TABLE 2. *Diseases Caused by the Virus of Herpes Simplex.*

Skin	Mucocutaneous Junction
Herpes simplex	Herpes labialis
Eczema herpeticum	Herpes progenitalis
Traumatic herpes	Vulvovaginitis
Mucous Membranes	Eye
Acute gingivostomatitis	Conjunctivitis
Recurrent stomatitis? ? ?	Keratoconjunctivitis
Central Nervous System	Generalized Infection
Meningoencephalitis	Hepatitis of newborn

The clinical pictures that can be caused by this virus in persons who react to their first exposure with illness show a wide variety (Table 2).

Recurrent Herpes

Most common are the familiar recurrent lesions about the mouth. They are characterized by grouped thin-walled vesicles on an erythematous base. The grouped arrangement of the vesicles is in contrast to the scattered arrangement that sometimes occurs on the skin of the face of a child with a primary herpetic stomatitis. It seems reasonable to suppose that the grouping means contiguous spread of the virus, whereas the scattering could mean that the virus was blood borne, or capable of infecting a number of different sites simultaneously. This

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would be unlikely to occur in the presence of circulating antibodies. In the child recurrent herpes of the skin of the face may be disguised by secondary impetiginization.

Acute Herpetic Gingivostomatitis

This is the commonest manifestation of primary herpetic infection and, also, is probably the most frequent cause of stomatitis between the ages of one and three years. Typically, a child in the second year of life begins to be very irritable and to have fever (the temperature is frequently as high as 105°F.) and refuses to eat, complaining of a sore mouth. On examination the entire mucous membrane of the mouth and tongue is involved with many or few lesions. The lesions are basically vesicles that have usually collapsed by the time they are seen, and the roof cells have become edematous so that the lesions appear to be covered with a yellowish-white, glistening membrane. Sometimes, the individual lesion is very large. It is only when this thick roof is rubbed off that true ulcers are seen. Two other clinical features of this primary stomatitis should be mentioned: the inflammation of the gums, which may vary from a thin line to intense swelling and redness, and enlargement of the regional lymph nodes. Although rare, cases sometimes occur in adults, presenting the same symptomatology as in the child.

Occasionally, the first lesions appear in the tonsillar region, and may be mistaken for a bacterial sore throat. Failure to improve on chemotherapy and the spread of the lesions to the rest of the buccal mucous membrane at length clarify the diagnosis. There is yet another condition that enters into the differential diagnosis when the lesions start on the throat, and that is herpangina — a disease caused by Group A Coxsackie virus. However, in herpangina, also, the lesions are practically confined to the posterior part of the mouth; furthermore, the disease is highly infectious so that there are other cases about and it occurs during the summer months.

The course of herpetic stomatitis lasts about seven days on an average, and the children usually begin to take food by mouth about two days earlier, even though the mouth still appears involved. There is no specific therapy for this self-limited disease; supportive measures consist of prophylactic penicillin, mouth washes in the older children, preferably of a solution of cetyl pyridinium chloride and local administration of tetracaine hydrochloride, if necessary. Supportive parenteral fluid therapy in infants may be required. No scarring results despite widespread involvement, and recurrent attacks are virtually nonexistent.

Herpetic Infections of the Skin

Next in frequency to stomatitis are the various types of primary skin involvement. Apart from the lesions that may accompany a stomatitis either on the face or on the fingers that are sucked, the most important is the involvement of the eczematous skin by the virus. This condition, which was first described most accurately by Kaposi[3] in 1887, has since been known as "Kaposi's varicelliform eruption." With Seidenberg's[4] isolation of the herpes virus from such a patient in 1941 it is probably wiser to call it "eczema herpeticum," particularly since the name Kaposi's varicelliform eruption is sometimes misapplied to patients with eczema secondarily infected with vaccinia virus, which in turn should be called "eczema vaccinatum." The differential diagnosis may be difficult, but observations concerning the following points should clarify the situation. First of all, invasion by either one of these viruses or a bacterium should be suspected when an infant with eczema suddenly becomes febrile and the character of the rash changes. Crusting may occur and may confuse the issue until the crusts are soaked off. When the essential lesion is established as being vesicular, an epidemiologic history is of the utmost importance. Definite exposure to a vaccinated sibling or an adult with "cold sores" will make the diagnosis almost certain. However, such a history is not always available. The character of the vesicles is important; in herpes they appear in crops for as long as eight or nine days, like chicken pox; the vesicles rupture and scab within a few days. The vesicles are single and scattered in the early stages of the disease but later become grouped. At any one time, therefore, the lesions appear at different stages. In vaccinial infection, however, they all appear to be at the same stage and look like the regular vaccination lesion.

Having suspected the diagnosis and perhaps confirmed it in the laboratory, as described below, the physician must next take stock of the patient's general condition. This disease varies in severity from an extremely mild to a fatal illness. In the severely ill patients, one must expect high, spiking fevers for eight or nine days, extensive loss of fluid and protein from the oozing skin surface, and the risk of a secondary bacterial infection. The treatment of all of this requires a well organized program of supportive measures, including fluid and electrolyte solutions and plasma or blood replacement as well as the use of antibiotics. Despite these measures occasional deaths occur. An illustrative case is afforded by an infant who appeared to be improving, but suddenly went into shock and died from a septicemia due to *Pseudomonas aeruginosa.*

Although eczema herpeticum is usually a manifestation of a primary infection, it may occur as a recurrent one in the presence of circulating antibodies. In the latter case, the systemic effects are mild.

In addition to the generalized skin involvement just discussed two manifestations of primary skin infection occur at times. One of these is known as

traumatic herpes. I have seen this after a graze of the hand or elbow or a cigarette burn of the hand. It is usually clear how this occurs since there is a history of cold sores in one of the parents at the time of the accident. A common, but not always hygienic, habit of "kissing the place better" would inoculate the virus directly onto the wounded skin. Clinically, these cases may be mistaken for herpes zoster since when they occur on a limb, lesions develop along that limb, more or less along a dermatome, and there is always an enlarged regional lymph node. In 2 patients observed during the acute attack, the diagnosis of a primary herpes-simplex infection was confirmed in the laboratory. In both cases the skin lesions were slow in healing, and recurrences were frequent at the site of the original lesion. In the child with the cigarette burn, the time relations are interesting. For two days after a cigarette burn, at the palmar base of the left third finger, the lesion appeared to be getting better. Then it became worse and vesiculated, and on the seventh day, other blisters appeared on the palm and up the arm and both epitrochlear and axillary nodes became enlarged. The patient had a maximum temperature of 102°F. and was irritable. Eight days after the beginning of the exacerbation a mild stomatitis that lasted only about four days developed. The hand finally healed three weeks after onset. Recurrences of grouped vesicles at the site of the burn were noted on several occasions during a period of two years after the primary occurrence.

An even less common observation is when a primary infection appears to occur on the unbroken skin.

Herpetic Infection of the Genitalia

Genital lesions of the recurrent type are not uncommon among adults of either sex. Penile lesions in children are extremely rare; I have never seen one, although Slavin[5] reported a case with tiny vesicles about the meatus and a watery urethral discharge. Primary herpetic vulvovaginitis occurs occasionally in children and must be considered among the differential diagnoses of genital lesions. The symptoms usually consist of discomfort to actual pain in the genitalia, perhaps a slight fever for a day or two and the appearance of, as one patient put it, "boils on the privates." Clinically, the lesions look very much like those in stomatitis, being collapsed vesicles, which soon ulcerate. Vesicles on the neighboring skin may help to make the diagnosis. Regional lymph nodes are enlarged. Autovaccination or accidental vaccination of the vulva may occur, posing an important point in differential diagnosis, which should be approached in the same way as that discussed under eczema herpeticum.

Herpetic Infections of the Eye

Recurrent herpetic involvement of the eye may occur at any age, and primary herpetic keratoconjunctivitis has been described, the enlargement of the regional preauricular node being of great aid in diagnosis.

Herpetic Encephalitis

Herpes virus is one of those invading the central nervous system and producing a meningoencephalitis. The original diagnoses were all made at autopsy. Recently, it has been realized that herpes can be the etiologic agent in patients with encephalitis who recover.[6] It has been stated that in one Italian series of meningoencephalitides, 7 per cent were due to herpes.[7] This antigen should be included in any diagnostic routine for the differential diagnosis of meningoencephalitis. Sufficient circumstantial evidence was available for diagnosis in 2 young children. One case was previously described.[2] The second patient was a nine-month-old infant who had fever, vomiting and sleepiness for three days before admission. Physical examination revealed bilateral conjunctivitis and a swelling in front of the right ear that was thought to be due to mumps but was probably caused by involvement of the preauricular lymph node. Serologic tests failed to demonstrate infection with mumps. The patient was irritable; a spinal tap revealed 147 lymphocytes per cubic millimeter, with normal sugar and protein. There was a sharp rise in antiherpes antibodies between the fourth and twenty-first days after the onset of the illness. Recovery was slow, and bilateral subdural hematomas were found and evacuated. Final recovery appears to be complete. Unfortunately, no attempts were made to isolate the virus.

Generalized Illness

From the description of several of these clinical pictures, it will be clear that there is often a severe systemic reaction. It seems probable that this may be associated with a viremia, which has been demonstrated in several patients with severe eczema herpeticum[8] and in 1 patient with a primary infection of the nostril.[9] Many other attempts have been negative, but it seems reasonably certain that a viremia of greater or lesser severity occurs during the primary illness. In the past, there have been reports of generalized grippe-like illness occurring among adults as a result of this virus. However, of much greater moment to pediatricians are the reports[10-12] of an overwhelming herpetic infection in newborn infants, either premature babies in whom there was no associated illness in the mothers or in those delivered at full term whose mothers had had a herpetic infection immediately before the birth. These illnesses are characterized by a vesicular eruption of the skin, profound toxemia and jaundice. Autopsy shows hepatitis, pneumonitis and encephalitis due to the herpes virus. The extensive involvement of the liver has given rise to the term herpetic hepatitis. A terminal septicemia caused by *Pseudomonas aeruginosa* may occur.

Diagnosis

The diagnosis of the diseases caused by this virus can be made with the use of four possible technics.

Isolation of the Virus

This can be done by inoculation of material from vesicle fluid, saliva or the internal organs at autopsy in a suspected case onto either the chorioallantoic membrane of the embryonated chick, onto the cornea of the rabbit or into suckling mice intraperitoneally. If virus is present, the chorioallantoic membrane shows the development of characteristic small, oval pocks, which are quite different from the large, round ones caused by vaccinia virus. In the rabbit, a keratoconjunctivitis results that cannot be distinguished from that caused by vaccinia virus, but with herpes infection an encephalitis often develops after a few days. Suckling mice die with or without preceding paralysis.

Serologic Tests

As in the diagnosis of any virus disease, the important observation is the comparison of the titer of antibodies in serum taken at the beginning of the illness with that in serum drawn during convalescence. In primary herpes infection both neutralizing and complement-fixing antibodies are measured. From the point of view of the best liaison between the clinician and the laboratory, knowledge concerning the behavior of the antibodies after infection is of great importance. Both types of antibody begin to rise steeply on the fifth day after infection so that it is important to obtain the first serum as soon as possible after onset. In contrast to the change in antibodies that results from a primary infection, it is interesting that in the previously infected adult, as mentioned above, no significant change in antibody titer follows an attack of herpes labialis, regardless of the frequency of attacks.

Histology

Since herpes infection often causes a superficial lesion it is not difficult to obtain biopsy material for a diagnostic study. The histologic findings of superficial lesions are those of vesicle formation appearing in the prickle-cell layer of the epidermis. There is ballooning degeneration of the epithelial cells at the margin of the vesicle. The vesicle fluid contains desquamated epithelial cells, including the so-called virus multinucleated giant cells, which are of great importance diagnostically, as indicated below. The histologic picture of the vesicle of the mucous membrane is modified by the environment so that it ruptures early, with loss of fluid, and there is swelling of the roof cells. These modifications give rise to the characteristic appearance of the lesions in the patient. The nuclei of the involved cells contain the typical inclusion body that is only found in herpes-simplex and in herpes-zoster and varicella infections. Recent work suggests that these inclusion bodies actually contain the herpes virus at one stage.[13] Although there is capillary dilatation and leukocytic infiltration of the corium, there is no necrosis so that scarring is usually absent.

The presence of giant cells can be used as an aid to diagnosis since these only occur in herpes simplex or herpes-zoster and varicella infection and not in vaccinia. They can be identified in a Giemsa-stained smear made from the scraping of the floor of a fresh vesicle, although the inclusion bodies themselves cannot be seen clearly with Giemsa stain.[14]

Electromicroscopy

Naturally, this can hardly be classed as a routine diagnostic tool, but it has been used, to my knowledge, on one occasion for the diagnosis of a vesicular lesion of the vulva; extension of the procedure in similar cases is possible. The electron microscope shows the herpes-simplex virus to be a spherical particle that rapidly undergoes some sort of dissolution in the center, giving rise to a doughnut appearance.[15] On examination of thin sections of infected cells particles of this sort can be seen within the inclusion body.[13]

Treatment

Some reference to treatment was made in the discussion of the various clinical entities. Several points should be given consideration. First of all, there is no specific treatment. Antibiotics are essential in the handling of secondary infection, but do not have a direct action on the virus. Supportive therapy is of the utmost importance in the handling of severe cases of eczema herpeticum, and of infants dehydrated from fever who are unable to take fluid by mouth because of pain. As mentioned above, cleansing mouth washes and local administration of Pontocaine may be tried in stomatitis, but the most practical thing is to pamper the child's whims regarding food and fluid. Cold semisolids like ice-cream are often most readily taken. In the management of adult patients in whom frequent recurrences of herpes occur without any of the usual stimuli such as fever and sunburn, it is well to consider psychiatric help. Blank and Brody[16] studied a number of such patients and found them all to be highly suggestible people whose herpes stopped with superficial psychotherapy. This may explain the varying success that has been reported with the use of smallpox vaccination or x-ray for such people. The enthusiastic proponent was successful, and the skeptic was not. Naturally, the pediatrician's concern with these people is to control a possible source of infection that may cause the appearance of clinical herpes among his child patients.

Epidemiology

The epidemiology of herpes infection illustrates the high degree of mutual tolerance that has been achieved in this host-parasite relation. A serologic

survey of children and parents in a low socioeconomic group coming to the Outpatient Department of the Children's Hospital of Philadelphia revealed the following situation. Among adults, neutralizing antibodies were found in the blood in 63 per cent. In infants up to four months of age, the incidence was the same, as would have been expected from the presence of passively transmitted antibodies. Between the ages of four months and two years, the figure dropped to about 5 per cent; this age group, of course, provides the major pool of susceptible persons, among whom the clinical manifestations discussed above are largely encountered. It is worth mentioning, however, that for some reason clinical cases are rare before the age of one year, an observation also made by Anderson and Hamilton[17] in a study in Australia. This may mean that effective but technically undetectable quantities of transmitted antibodies persist for another six to eight months or that other factors enter into the initiation of an infection, such as the trauma of teething. Between the ages of two and five years the rate of infection increases rapidly so that by the latter age the incidence is the same as that among the adults in the community.

When this pattern of infection was compared with the incidence of the most common clinical manifestation — namely, herpetic gingivostomatitis — it was surprising how low the frequency was. For a year my colleagues and I saw all the patients with stomatitis coming to the Outpatient Department — a total of 38 cases among 5000 patients under five years of age. If 60 per cent are assumed to have been infected, clinical symptoms developed in only 1.3 per cent. Naturally, patients with mild cases would not be brought for treatment, and some could have been overlooked; this figure is certainly lower than the true one. Shortly after this analysis, some friends of mine started a painstaking health survey of 1000 babies in Newcastle, England. These infants were to be followed from birth to five years. An analysis of the clinical incidence of stomatitis among that group showed a total of 85 cases among 950 children in the first five years of life, or an incidence of clinical symptoms in 15 per cent of those infected, if one assumes the same infectivity rate as in Philadelphia.

It seems, then, that well over 80 per cent of primary infections are subclinical in the average community. This experience is not universal, however, since, in the crowded environment of an orphanage in Australia, Anderson and Hamilton[17] found an incidence of stomatitis of 56 per cent, and a 100 per cent infection rate among their susceptible patients by the time they were five years old. Environmental circumstances of this sort may account for the family epidemic occasionally encountered in which clinical stomatitis occurs in each member of the family in turn. The average incubation period in Newcastle was reported as seven days, but it may be as short as two days. It is not known just what factors determine whether a person is to get a clinical or a subclinical infection. As a preceding incident to the onset of clinical stomatitis trauma — such as cutting of teeth or, in an adult, vigorous gum massage — or an upper respiratory infection was frequent. It also seems that clinical stomatitis occurs mainly in the season of respiratory illness.

The mechanism of spread of the disease is not altogether clear. Virus is found in the saliva and stools of patients with herpetic stomatitis. Furthermore, virus can be isolated from the saliva of persons without evidence of infection. The incidence of such asymptomatic carriers, according to Buddingh et al.,[1] ranges from 20 per cent among children seven months to two years of age to 9 per cent among those from three to fourteen years and 2.5 per cent among adults. It seems probable that intimate contact is the most important factor in the spread of virus. This would account best for the altered incidence found with varying socioeconomic levels. It has been recorded by several observers that the incidence of infection is highest in the lower socioeconomic levels, where crowding and poor hygiene are greatest, and lowest among persons of higher levels. Burnet[18] has commented on the effect of improved public-health measures in Melbourne, Australia. He found an incidence of 90 per cent among the poorer sections of the population in 1940 but one of only about 60 per cent in 1950. In the intervening decade, great strides had been made in education of the public in matters of hygiene through well-baby clinics. Infancy is the period during which there is the greatest bodily contact with other people, and this is probably a large factor in the rapid spread of infection in that age group. As for cases occurring among adults, to which I have referred earlier, sexual contact is probably the most potent factor.

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CHECKREIN SHOULDER*
A Type of "Frozen" Shoulder
Diagnosis and Treatment by Manipulation and ACTH or Cortisone

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TWENTY years ago Codman,[1] in his classic work on the shoulder, described "frozen" shoulder as "difficult to define, difficult to treat, and difficult to explain from the point of view of Pathology." Since then progress has been made, but the problem remains far from solved.

Etiology, in particular, is not clear. The condition occurs in middle life, more often in women than in men. It has been well established that arthritis and other general metabolic diseases play no part. Major trauma is rarely a factor. Rupture of the supraspinatus tendon and the other elements of the rotator cuff, although painful, is never accompanied by limitation of passive motion. McLaughlin and Asherman,[2] in several hundred shoulders operated on for various reasons, found no torn cuff associated with a stiff shoulder and no stiff shoulder associated with a torn cuff.

On the other hand, the initiating episode in most cases is a minor contusion or wrench, or an episode of inflammation. Usually, the inflammation is sterile, occurring about a calcific deposit in the rotator cuff; occasionally, it is bacterial, accompanying an infected hand or arm.

In a few cases, notably those appearing after coronary thrombosis, there apparently is no initiating episode except pain.

Invariably, the onset is followed by a period of disuse, imposed by pain. This is the only constant factor in all cases. The arm is held to the side, and the forearm across the chest in a sling until the inflammation or trauma has run its course and pain has subsided, usually a matter of weeks rather than days. Thereafter, varying degrees of painless abduction and rotation return, but presently the situation becomes static, and further motion is not recovered. Pain occurs principally on attempts to move beyond a certain point.

On examination varying degrees of limitation and varying resistance to passive manipulation are encountered. However, most patients present a remarkably consistent pattern of pain-free passive motion sharply checked at about 45° of true abduction of the humerus on the scapula and about half the normal range of rotation.

Atrophy of shoulder-girdle musculature roughly parallels the duration of symptoms. There is usually no tenderness, and peripheral nerves and blood vessels are normal. X-ray examination discloses only osteoporosis from disuse and, in about 20 per cent of cases, calcific deposits in the inner-cuff tendons.

As in other poorly understood conditions, for which treatment has not been very satisfactory, the patient has been blamed for his own plight and psychosomatic factors have been suspected. It is, however, probable that the "periarthritic personality"[3] is at least as often the result of the painful stiff shoulder as its cause.

The pathology has been variously described by Codman,[1] and by Moseley[4] as consisting of adhesions across the subdeltoid bursa, by DePalma[5] as "extra-articular and intra-capsular adhesions," by McLaughlin[6] as contracture of the subscapularis and biceps tendons, and by Neviaser[7, 8] as adherence of the anterionferior folds of the joint capsule to each other and to the adjacent glenoid and humerus.

The most generally accepted treatment consists of gradual stretching by active exercise, accompanied by heat, x-ray therapy or repeated procaine infiltration. Such a program is safe and effective, but may require months and makes great demands on the patient's fortitude. Without treatment, disability may persist for months or years and can be permanent. McLaughlin[6] recommends surgical division of the subscapularis tendon and anteroinferior joint capsule in refractory cases.

Until recently, manipulation under anesthesia has been almost universally condemned as dangerous and futile.[6, 9, 10] As a rule pain after manipulation is so severe that active motion is difficult or impossible. By the time pain has subsided, adhesions and contractures can re-form, often with more limitation of motion than before manipulation.

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Clinical Studies and Results

Three years ago a study of the effect of ACTH on painful shoulders was undertaken.[11] It was quite effective in repressing pain accompanying the sterile inflammatory reaction about calcific deposits in the rotator-cuff tendons. In 2 cases of "frozen" shoulder, pain was repressed during the period of administration, but, as expected, the range of active and passive motion was not increased. In other words, ACTH could not dissolve the fibroblasts of established scar, adhesion and contracture. However, it seemed reasonable to assume that the pain that followed the stretching or tearing of soft tissues would be suppressed by the hormone. Accordingly, 6 patients with "frozen" shoulders were subjected to manipulation and were given ACTH for several days thereafter. The results were most gratifying; all 6 maintained the range of motion obtained at the operating table, and none required more than codeine for relief of pain.

The study has been continued and now includes the treatment of 29 shoulders in 26 patients, manipulated under anesthesia, given ACTH, hydrocortisone acetate or cortisone, and followed for at least three months.

Of these, 10 patients have regained painless, normal shoulder motion. Thirteen are improved, retaining some degree of pain, or limitation of motion, or both. Six are unimproved.

Seventeen patients were females, and 9 males. Right and left shoulders were equally involved. The average age was fifty and a half years, and the average duration of symptoms five and a half months. Calcific deposits were seen in the x-ray films of 6 patients.

The initiating episode was traumatic in 15 and inflammatory in 5 cases. In 6 there was apparently no initiating episode. These factors were essentially the same in the cured, improved and unimproved groups. In 5 patients the initiating trauma accompanied a thoracotomy on the same side as the involved shoulder, presumably the result of the position of the patient on the operating table.

Complications consisted of 1 case of sensory disturbance of the ulnar nerve, in which the patient recovered after several months and in which the manipulation itself was considered responsible, 1 case of psychosis, apparently precipitated by ACTH, that was treated successfully by psychotherapy, and 1 case of neurosis, with litigation overtones, that has not improved. No fracture or detectable disability from muscle or tendon rupture has occurred.

As experience accumulated it became clear that the patients who were completely relieved or improved presented such a regular pattern of symptoms and signs that it was possible to forecast a good result with assurance.

The salient points in the syndrome are as follows: a history of a disuse for two or more weeks after an episode of minor trauma, inflammation or pain; recovery of the lower ranges of shoulder motion during subsequent weeks or months, but pain on attempts to abduct or rotate beyond about half the

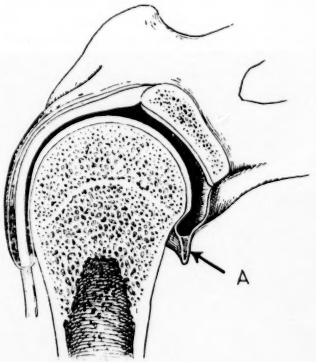

Figure 1. *Pathology of Checkrein Shoulder (Reproduced from Neviaser,[8] with the Permission of the American Academy of Orthopaedic Surgeons).*
Adhesion and contracture are apparent at A.

normal range; a sharp and definite check to passive motion at 45° of abduction of the humerus on the scapula and 50 per cent of internal and external rotation with the humerus in vertical position; and a single, definite, audible and palpable release of re-

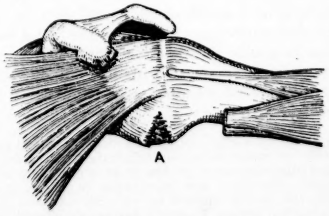

Figure 2. *Effect of Manipulation on the Checkrein (Reproduced from Neviaser,[8] with the Permission of the American Academy of Orthopaedic Surgeons).*

sistance at manipulation, followed by a free range of passive abduction and external rotation.

These findings are well explained by Neviaser's[7, 8] observation of 15 such shoulders manipulated after surgical exposure of the joint (Fig. 1 and 2). The contracted, adherent capsule was seen to tear and to strip from its attachment to the humerus. Nevi-

aser considered the term "adhesive capsulitis" more descriptive of the condition than "frozen shoulder." But "capsulitis" implies a process involving the whole capsule, and since only the anterior and inferior aspects are involved in a checkrein of contracture, the term "checkrein shoulder" is suggested. At present manipulation and administration of ACTH or cortisone are advised only for patients

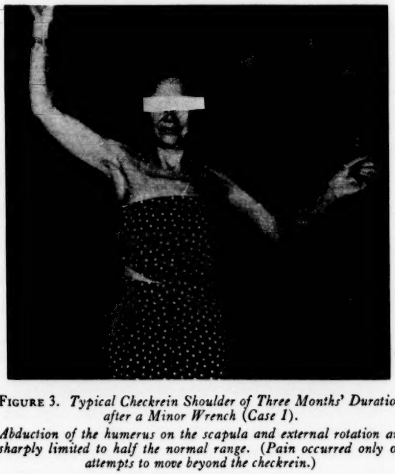

FIGURE 3. *Typical Checkrein Shoulder of Three Months' Duration after a Minor Wrench (Case 1).*

Abduction of the humerus on the scapula and external rotation are sharply limited to half the normal range. (Pain occurred only on attempts to move beyond the checkrein.)

with stiff, painful shoulders, whose symptoms and physical findings satisfy the criteria for checkrein shoulder (Fig. 3 and 4).

The following cases illustrate the syndrome of checkrein shoulder as it developed from minor injury, from inflammation about a calcific deposit in the inner-cuff tendons and from pain after coronary thrombosis.

CASE 1. D. C., a small, active, muscular, vigorous 44-year-old housewife, fell from a ladder, wrenching the left shoulder. Considerable pain was present for more than a week on any attempt at motion. Thereafter, the lower ranges of motion returned, but pain occurred on attempts to move beyond about half the normal range of motion. Passive abduction was sharply checked at 55°, and both external and internal rotation at about half the normal range (Fig. 3).

X-ray examination disclosed no variation from the normal in the bones of the shoulder girdle; 25 mg. of ACTH was given over an 8-hour period in an intravenous drip of 500 cc. of dextrose and water. On the following day on manipulation under anesthesia, 2 major releases of resistance were encountered in the arc of abduction between 50 and 75°. On recovery from anesthesia the range of motion was almost normal, being limited only slightly in abduction and internal rotation (Fig. 4). The same dosage of ACTH was given on the day of manipulation, and thereafter 20 units of ACTH gel was given for 4 days. No medication was required for pain. The patient was faithful with the exercise program she was taught, and 7 months later presented a normal, painless range of shoulder motion.

CASE 2. M. E., a 48-year-old, moderately obese spinster, had experienced several minor episodes of "bursitis" in the right shoulder over a 4-year period. A severe attack had occurred 4 months previously. Partial relief of symptoms followed novocain infiltration on several occasions, diathermy and x-ray treatment. X-ray study showed a moderate-sized calcific deposit in the rotator-cuff tendons at the greater tuberosity of the humerus. True abduction was sharply limited to 45°, external and internal rotation being restricted to about 75 per cent of normal; 25 mg. of ACTH was given in an 8-hour infusion of dextrose and water. On the next day several distinct releases of resistance were encountered in the arc between 50 and 75° of abduction. Fairly severe pain occurred immediately after manipulation and was relieved within an hour by another intravenous infusion of 25 mg. of ACTH. A similar infusion was given on each of the 4 following days and ACTH gel, 20, 10 and 5 mg., on the next 3 days.

After the last dose of ACTH the patient exhibited a fairly marked depression, which persisted for several weeks. Shoulder

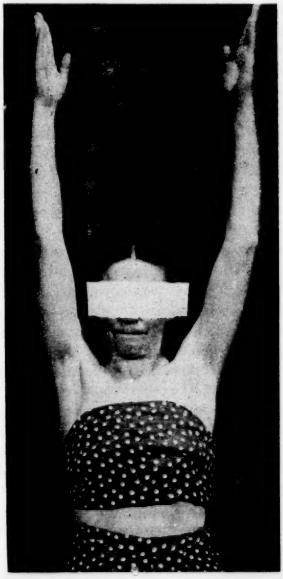

FIGURE 4. *Checkrein Shoulder Three Days after Manipulation (Case 1).*

Active motion is painless and almost normal in range. A single release of resistance occurred at manipulation. Pain was suppressed by intravenous injection of ACTH.

motion returned almost to normal, with only slight limitation of internal rotation but with moderate pain particularly in the mornings. The depression responded to psychiatric treatment. This patient was classified as improved 8 months after manipulation.

CASE 3. A. P., a 55-year-old tailor, had an acute coronary thrombosis and was hospitalized for 8 weeks. Pain during this period was present in the precordium, left deltoid region and inner aspect of the elbow. The patient did not move his arm during the first 8 weeks after the onset of pain. Thereafter, as his heart condition gradually improved, the lower ranges

of shoulder motion returned, but pain occurred on attempts to move beyond about half the normal range of abduction, external and internal rotation. Treatment included infiltration of the lumbar sympathetic chain for "shoulder-hand syndrome" on 4 occasions, a course of cortisone and nitroglycerin, all without relief. Forty units of ACTH gel was given twice during the 24 hours before manipulation. At manipulation a single release of resistance occurred in the arc between 45 and 60° of abduction. On recovery from anesthesia pain had disappeared completely. No medication was required, and 3 months later the range and power of motion of the shoulder girdle were normal and the patient had returned to work.

The histories and physical findings of the 6 patients who were not relieved or improved did not present a consistent pattern, and at manipulation varying degrees of resistance and release of contracted tissues were encountered. The following cases are illustrative.

Case 4. W. C., a 59-year-old workman, sustained a contusion of the left shoulder girdle and brachial plexus from a heavy falling object. Examination several weeks later showed fairly marked atrophy of the deltoid and rotator muscles and a bizarre pattern of motor and sensory involvement of the brachial plexus involving principally the posterior cord and reflected primarily in a paralysis of the radial nerve. There was almost no active or passive motion possible at the shoulder. The brachial plexus was explored through an anterior incision, and no gross abnormality found. The radial nerve at the elbow was also explored, with similar normal findings. For 2 weeks after operation the arm was bound to the side. Thereafter during the next six weeks about 40° of abduction, 15° of external rotation, 75° of flexion and 40° of extension were regained and gradual improvement in nerve function occurred. The patient was readmitted to the hospital and given 25 mg. of ACTH in an 8-hour infusion of 500 cc. of dextrose and water. On the next day such resistance was encountered, presumably from postoperative contracture of the pectoral and subscapularis muscles, that the manipulation was abandoned with no appreciable gain. ACTH was continued for 4 days together with vigorous physical therapy. During the subsequent 6 months the paralysis of the radial nerve disappeared, and the patient regained about a third of his shoulder motion but has little pain and is able to work.

If greater force had been employed in manipulation of this shoulder, a fracture of the humerus would almost certainly have occurred.

Case 5. E. S., a 54-year-old housewife, complained of gradually increasing pain and limitation of motion in the right shoulder of 5 months' duration. X-ray examination disclosed a calcific deposit in the rotator-cuff tendons. X-ray therapy was given, without relief. Pain was present at any attempt to move. True abduction was limited to 10°, external rotation to 5° and internal rotation to 30°. At manipulation a fine, crepitating resistance was encountered throughout the range of abduction and external rotation. No ACTH was given before manipulation; 25 mg. was given daily in an intravenous infusion of 500 cc. of dextrose and water over a period of 8 hours for the next 4 days. One dose of meperidine hydrochloride (100 mg.) was given for pain on the day after manipulation. Any exercise was accompanied by pain. Eventually, about 50° of true abduction and about half the normal range of rotation returned. Although the patient thought that she was considerably improved, the result has been classified as poor.

The diagnosis in this case was wrong. A smoldering inflammatory process was present, and the resistance encountered on examination and at manipulation was that of muscle spasm rather than established scar forming a checkrein.

Preparation, Procedure and Aftercare

At the beginning of the study it was believed that considerable stimulation of the adrenal cortex would be required to suppress reaction and pain after manipulation. Accordingly, ACTH rather than large doses of cortisone was chosen. The first few patients received 25 to 40 mg. of ACTH intramuscularly every six hours, the administration beginning twenty-four hours before anesthesia and continuing with gradual diminution of dosage for seven to ten days. A low-sodium diet was given, and during the period of active adrenocortical stimulation, daily supplements of potassium in the form of enteric-coated tablets of potassium chloride (0.9 gm. three times daily). Later 20 mg. of ACTH dissolved in 500 cc. of 5 per cent dextrose or saline solution was given daily as an intravenous infusion over a period of eight hours, for three or four days, followed by decreasing daily

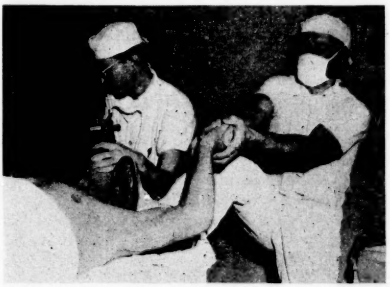

Figure 5. *Wrong Way to Manipulate a Shoulder. Too much unguided force is being applied, and the arm is being used as a lever.*

intramuscular doses for three or four more days. When it became clear that the vigorous adrenocortical stimulation of intravenously administered ACTH was not necessary, a pure form of ACTH gel, which releases the hormone at a fairly constant rate, was employed. The minimal effective dose was found to be 40 mg. intramuscularly twice daily, beginning twenty-four hours before manipulation and continuing for three days. For three more days, decreasing doses of 30, 20 and 10 mg. were given.

Two patients received 200 mg. of hydrocortisone acetate, injected into the shoulder joint and subdeltoid bursa at the time of manipulation. Both experienced fairly severe pain and required ACTH for relief.

The last four patients received cortisone by mouth, 300 mg. daily in divided doses on the day before manipulation and for the next three or four days. Thereafter, the dosage was tapered for another three or four days.

Established contraindications to ACTH or cortisone, such as recognizable psychoses, active peptic ulcer, active tuberculosis, syphilis or other infection, bleeding tendencies and marked congestive

heart failure or hypertension, were ruled out in every case. Up to the present, patients have been hospitalized throughout the period of treatment. It is hoped, however, that hospitalization for the average patient in good general health can be reduced to two or three days, with subsequent outpatient or office observation.

The manipulation itself cannot be considered lightly. It is a blind procedure, fraught with considerable potential danger (Fig. 5). The clearly audible, tearing release of the checkrein can be most disturbing to the surgeon, who cannot see what is happening beneath the intact skin. Gentleness in the application of force is essential. The patient's arm should not be used as a lever. The humerus should be grasped just distal to the axilla, and the operator's forearm should press equally at all points against its length. The other hand depresses the shoulder and restricts rotation of the scapula (Fig. 6).

FIGURE 6. *Correct Method of Manipulation.*
The operator's forearm exerts pressure along the whole length of the humerus, and his opposite hand restricts rotation of the scapula.

The humerus is gently but firmly abducted through the 10 to 20° occupied by the checkrein. When free passive abduction has been achieved, external rotation will usually be found to be restored to normal. Occasionally, further gentle manipulation of external rotation will be required. No attempt is made to increase the range of internal rotation, lest the atrophic, contracted rotator-cuff muscles and tendons be torn. The procedure requires no more than three or four minutes. Pentothal anesthesia is used in all cases.

An intensive program of active motion begins as soon as the patient recovers from the anesthetic. Every doctor, nurse, physical therapist and attendant who sees the patient encourages active motion in the previously restricted range. Between periods of activity, rest with hands clasped behind the head is encouraged, since this position requires the maximum of external rotation and abduction.[12] At least twice daily the patient spends thirty to forty-five minutes with the physical therapist in guided exercise with the assistance of counterweights. Heat, in the form of simple wet packs, may precede these exercise periods. Before discharge from the hospital an exercise program requiring fifteen minutes each night and morning is taught, and the patient is urged to continue the program indefinitely.

SUMMARY

The natural history and treatment of "frozen" shoulder is discussed.

Experience with the treatment of 20 "frozen" shoulders by manipulation and suppression of pain after manipulation with ACTH and cortisone is presented. Ten patients regained normal painless shoulder motion; 13 were improved, and 6 unimproved.

The term "checkrein shoulder" is suggested for the consistent pattern of history, physical findings and response to manipulation encountered in the 23 patients who were relieved and improved.

The technic of manipulation and the details of administration of ACTH and cortisone are discussed.

I am indebted to Drs. George W. Thorn, Albert E. Renold and David H. P. Streeten for their enthusiastic co-operation in the administration and evaluation of ACTH and cortisone.

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RADIATION THERAPY OF SOME DERMATOLOGIC DISORDERS*

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THE discovery of x-rays by Roentgen in 1895 opened a new epoch in the field of medicine. These rays were soon used for diagnosis and treatment, and today ionizing radiations hold a preeminent position in dermatologic therapeutics. Perhaps the most important therapeutic agent in the armamentarium of the dermatologist is the x-ray machine. The dermatologist recognizes the inherent dangers pertaining to the use of all forms of ionizing radiations; yet their proper use renders these agents safe.

Formerly, x-rays were used for the treatment of many dermatoses for which there are better methods of treatment today. Erysipelas, for example, responds so well to penicillin that radiation therapy is hardly ever used. In fact the incidence of erysipelas has decreased markedly as a result of the widespread use of antibiotics before and after operation and whenever the presence of an infection is suspected.

Ignorance, faulty technic, overirradiation, underirradiation, improper selection of wave qualities, improper intervals between doses and other faults have done much to discredit the usefulness of superficial x-ray therapy. I am convinced that x-rays are still useful and safe for the treatment of many cutaneous abnormalities that would otherwise respond poorly or not at all to other methods of treatment.

The ionizing radiations employed most commonly in dermatology are roentgen rays. Radium is used far less frequently than x-rays and almost exclusively for cavernous hemangiomas and epitheliomas. Only a few dermatologists employ radium needles interstitially for the treatment of cutaneous neoplasms. The radioactive isotopes have not, as yet, been found of great value by either surface or internal application in the treatment of skin diseases. Thorium-X has been used successfully for the treatment of localized patches of neurodermatitis, lichen planus, psoriasis and keratoses. It is claimed that thorium-X improves or cures poikiloderma and nevus flammeus. My experience with this agent leads me to doubt its efficacy in the treatment of these two diseases. Likewise, I seriously question the rationale of thorium-X for the treatment of acute or chronic radiodermatitis. Again, my experience and knowledge of ionizing radiations lead me to believe that thorium-X would aggravate rather than ameliorate any form or degree of radiodermatitis. Even though some superficial epitheliomas may involute when treated with thorium-X I should feel as though I were toying with an epithelioma if I treated it with thorium-X. Cutaneous cancers may be very deceptive in type and depth and area of involvement and therefore require treatment whether it is surgical or radiation with such vigor as to assure cure the first time that they are treated. Every physician owes to his patients the type of treatment for cancer that would eradicate it completely, quickly and with minimal mutilation. In my opinion thorium-X, with its predominance of nonpenetrating radiations, is not a suitable agent for the treatment of cancer of the skin.

Grenz rays, which are x-rays of extremely long wave lengths and having a half-value layer of approximately 0.035 mm. of aluminum, are becoming more popular. They are produced with kilovoltages varying from 8 to 15. The modern tubes are air cooled and have a window of beryllium or thin glass. Because of the extreme softness of these rays, they are incapable of penetrating through tissue. All but 15 per cent of the incident beam is absorbed in the first millimeter of skin. Therefore, a papule or a vesicle or any other lesion with a diameter of 0.5 mm. receives only 35 per cent of the incident beam at the base. Most skin lesions reach to a depth of 3 mm., where only 3 per cent of the surface dose penetrates. If 300 r is to reach a lesion 3 mm. in diameter, it is necessary to apply a dose of 30,000 r at the surface. This is sure to cause permanent radiation changes, especially hyperpigmentation and telangiectasia. At least one dermatologist has said that he has applied 50,000 r in divided doses for the treatment of an inflammatory lesion to the scalp without damage of any kind. It may be so, but I have given one dose of 600 r to an area on the forearm of 1 square inch and permanent telangiectasia resulted. I firmly believe that the concept of using unlimited amounts of grenz rays for the treatment of recurrent inflammatory dermatoses is wrong. Furthermore, the practice is dangerous in the sense that it results in permanent pigmentation and telangiectasia. I think that these permanent changes on any part of the body, especially of the face, are unwarranted. Such a case was recently presented at one of the local dermatologic meetings in New York in which a girl had been treated with grenz rays for keratosis follicularis. The condition improved, but there were hyperpigmentation and telangiectasia. I think that the radiodermatitis is relatively more dangerous and more serious than the keratosis follicularis.

It has been claimed for at least twenty years that grenz rays are specific for the treatment of nevus

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flammeus. I have used grenz rays for the treatment of this condition, and I have never been able to improve a single lesion. If one treats nevus flammeus sufficiently early in life, improvement may be seen in the lesion, but in such cases the improvement should be ascribed to time rather than to grenz rays because with the passage of time many light lesions of nevus flammeus improve.

Grenz rays have no specific biologic effects that are not common to all ionizing radiations. Grenz rays are useful for the treatment of superficial dermatoses involving the scalp, eyelids and genital areas and also for recurrent pruritic dermatoses and for inflammatory eruptions in children when it is necessary to protect epiphyses. The total doses and intervals of treatment should be in general the same as those for harder radiations.

Many diseases of the skin respond to superficial x-ray therapy. Only a few illustrative conditions in different categories are dealt with here.

Acne vulgaris is one of the most common diseases that the dermatologist is called upon to treat. Patients are often treated by the family doctor, the allergist, the gynecologist, the endocrinologist and the beauty counselor. Finally, the patient with severe acne vulgaris gets to the dermatologist. Judicious and proper combined treatment instituted early could prevent pits, scars, disfigurement, discouragement and even depression.

Many cases of acne vulgaris can be cured without the use of x-rays. However, cases that show a tendency to rapid spread and leaving deep pits and scars when the pustules involute and those in which the deep pustular element is pronounced or in which acne cysts are forming, as well as all cases of acne conglobata, should be given the advantages of x-ray therapy along with other appropriate topical remedies and systemic and general treatment such as diet, antibiotics and hormones. I have seen no evidence that x-ray therapy predisposes one to greater scar formation. Early or late radiation sequelae should never occur.

For the past twenty years, I have adhered to more or less the same technic. I usually apply to each side of the face, after appropriate shielding of the hair, eyes and lips, 75 r of low-voltage, unfiltered x-rays having a half-value layer of between 0.5 and 0.75 mm. of aluminum. This type of radiation is obtained from conventional superficial therapy apparatus. If a beryllium window tube is used a filter of 0.5 mm. of aluminum is inserted between the patient and the tube. The patient is treated each week up to a maximum of 16 treatments over a period of twenty-four weeks. At first the treatments are given weekly, and later the interval is increased. In some cases, in which erythema develops even after 2 or 3 treatments, the x-ray applications are stopped, being resumed when the reaction subsides if the indications still warrant this therapy. In other cases it is necessary to give more than 16 treatments; the patient is kept under treatment with modalities other than x-rays for a period of a year and then the x-ray treatments are resumed. Occasionally, it is necessary to give an additional course of 16 treatments over a period of approximately thirty weeks. I have particularly observed patients who received up to a maximum of 2400 r each year; some have been seen twenty years after cessation of treatments and no deleterious effects from the x-rays were observed. This statement is not to be construed as advocating that it is safe to administer 32 fractional doses of x-rays in successive weeks for the treatment of acne vulgaris. In fact this applies only to the occasional case of acne.

When the back and chest are involved, they are treated at the same time that the face is exposed. There is no danger of affecting the hemogram or of inducing other deleterious effects when the face, chest and back are exposed on the same day. Care is to be taken to avoid excessive overlapping. The acne generally involves only the sternal area, and it is therefore necessary to expose only the midsternum. On the back, however, it is necessary usually to expose the area of each shoulder and the midportion of the back about the region of the first lumbar vertebras. If these points of exposure are measured the distance between focal points should be between 25 and 30 cm. The focal skin distance should be no less than 20 and no more than 30 cm. In this way the amount of radiation falling between focal points will approximate that of the focal points.

Tinea capitis caused by organisms that do not respond to topical remedies such as *Microsporum audouini*, *Trichophyton tonsurans* or *T. schoenleini* should be treated with x-ray epilation to obtain a quick cure and prevent the spread of the disease to epidemic proportions. Children with this disease should be isolated without delay. As soon as the diagnosis is made and the organism has been identified, x-ray treatment should immediately be instituted in all noninflammatory types of the disease. Isolation in special classes or special schools is unnecessary if proper treatment is instituted early. The use of many hundreds of fungicidal ointments has been successful in degrees varying from 10 to 100 per cent. Waiting for immunity to develop or waiting for spontaneous cure to develop at puberty is uncertain and unscientific, since in the meantime the infected child may contaminate dozens of other children.

Temporary epilation with x-rays is a safe procedure provided that it is properly carried out and the apparatus is properly calibrated according to accepted physical and biologic standards. This treatment cannot be performed by a novice or anyone with mere "book knowledge" unless he is properly supervised by someone experienced in this technic. I have personally treated or supervised the treatment of thousands of cases of ringworm of the

scalp, and I have never observed any immediate or late deleterious effects.

The most practical technic is the Kienböck–Adamson five-point method, and to each point an epilating dose of approximately 300 r is applied. There is a difference in the numerical value of the epilating dose because different iontoquantimeters give different values for the roentgen output. This can be easily demonstrated if different ionization chambers are put in the same x-ray beam. One will readily see the wide variation in readings. That is why one must corroborate physical measurements with biologic test materials.

Failure to cure after x-ray epilation is due to failure to carry on follow-up treatment, which consists of removal with epilating forceps of all fluorescent hairs seen under the Wood light before the new hair starts growing in. Mildly fungicidal ointments should be applied for several weeks after every fluorescent hair has been removed. These broken-off hairs lie in the follicles and require mechanical removal.

I am often asked when is it safe to apply a second epilating dose of x-rays. This is a difficult question. One should wait until there is complete regrowth of hair. It seems to me that at least six months should elapse before a second and at least one year before a third epilation is attempted. This is really an academic question because the first dose should be sufficient for a cure especially if a modern, properly calibrated x-ray machine is used.

There is considerable controversy regarding the treatment with x-rays for symptomatic relief of such recurrent chronic and pruritic dermatoses as neurodermatitis, psoriasis, lichen planus and pruritus ani and vulvae. These diseases should not be treated routinely with x-rays. However, there are times when a particularly severe attack may be terminated quickly by the application of a few weekly fractional doses. The danger is in applying to the same areas repeated courses of treatment; if careful records are kept and the amount of radiation is kept down to 4 to 6 treatments in any one year to any one area, such courses can be repeated for at least eight years without causing injuries. Harm results only when the issue is forced with the x-rays.

Neurodermatitis and psoriasis sometimes become so extensive that the eruption is universal. They may simulate an exfoliative dermatitis. In these cases the pruritus is severe and the discomfort unbearable. As an adjuvant to other methods of treatment, x-ray therapy often yields gratifying results. One third of the body is treated every other day with fractional doses. No one area receives more than 75 r each week. The white-cell count is lowered after a month of such treatment but not alarmingly so, especially if the kilovoltage is lowered to about 60.

The use of x-rays for the treatment of pruritus vulvae of a pregnant woman should be scrupulously avoided, not that there is danger of deleterious effects on the fetus from the use of low-voltage radiations but because of possible medicolegal involvement. No matter what abnormality is noted at birth, the blame will in all likelihood be placed on the treatments administered. In fact I avoid using x-ray therapy for any condition in a pregnant woman.

Perhaps the greatest field of usefulness of x-rays is in the treatment of the lymphomas, especially mycosis fungoides and leukemia cutis. Leukemia cutis is rare, but there are cases in which there is no evidence of leukemia anywhere in the body except in the nodules of the skin, and then months or years later, the blood and the lymph nodes show definite signs of involvement. The cutaneous nodules respond remarkably well to irradiation. When the nodules are small and scattered over large areas of the body, it is necessary to divide the body into thirds and treat a third every other day as is done with widespread inflammatory dermatoses. A dose of 75 to 100 r is generally sufficient for resolution. When the nodules are large and there are only a few of them a single dose of 200 to 300 r once every two weeks to each lesion, closely shielded, suffices. Sometimes the lesion responds to one treatment, and in other cases several doses are required. Conventional superficial therapy is employed in most. The deeper lesions require a filter of 1 to 3 mm. of aluminum, depending on the thickness.

Mycosis fungoides presents a unique problem. There is no agent that is as effectual in prolonging life and ameliorating lesions as x-rays. Nitrogen mustard, tartar emetic and radioactive phosphorus are inferior to and more hazardous than x-rays. Patients with extensive lesions are treated in the same way as those with universal dermatoses. However, most patients with mycosis fungoides have a few scattered tumorous lesions, which are treated separately. The normal surrounding skin is shielded, and many tumors respond to a single dose of 200 to 300 r of conventional low-voltage x-ray therapy. Only the thicker lesions require a filter of 1 to 3 mm. of aluminum. Occasionally, 3 or 4 treatments administered once every two weeks are necessary. Some of the rapidly growing ulcerative lesions require tremendous doses of highly filtered x-rays, and even this does not stop the progress of the disease. Ordinarily, however, mycosis fungoides responds very well to relatively small doses. The treatments have to be continued as long as new lesions develop. It is remarkable how rarely radiodermatitis is seen in patients with long-standing mycosis fungoides. Eventually, lymphosarcoma or reticulum-cell sarcoma develops in many areas of the body, and death soon ensues.

Idiopathic multiple hemorrhagic sarcoma of Kaposi is a rare disease and usually has only cutaneous manifestations. However, some patients have

multiple foci in various organs. The concept at present is that in each focus the disease begins there alone — in other words, it is not metastasizing. The cutaneous lesions may be present in a quiescent state for many years, showing little or no activity. Finally, however, lesions develop in vital areas of the body, and the patient finally succumbs. In some cases either lymphosarcoma or some other lymphoma occurs in patients who have had Kaposi's sarcoma for years.

There is no therapeutic procedure that gives such satisfying results as x-rays. When the lesions are superficial and multiple and involve an extensive area of an extremity, the whole extremity is exposed to radiations from a conventional superficial apparatus. Doses of 75 to 100 r are given at weekly intervals. When the tumors are large, deep and scattered they are treated individually. Normal surrounding skin is well shielded with lead foil, and doses of 200 to 300 r are administered at weekly or at biweekly intervals for a total of four to six treatments. Kaposi's sarcoma is relatively radiosensitive; it is rarely necessary to give as many as six treatments. Occasionally, ulcerative lesions occur and respond poorly to radiation alone. Supportive treatment with the use of elastic bandages and elevation of the extremities is helpful. When the disease involves many areas of the body, including the viscera, the prognosis is poor, and very little can be expected from radiation therapy. In some cases amelioration of the disease has followed therapy with the radioactive isotopes. It cannot be said that x-ray therapy cures patients with Kaposi's sarcoma, but I am convinced that there has been symptomatic improvement and prolongation of life in many cases.

One of the earliest lesions to be treated soon after x-rays were discovered was carcinoma of the skin. It was soon learned that all types of cutaneous cancers exclusive of the melanomas responded extremely well to irradiation, and for a time x-rays were the method of choice. Now, however, this is not necessarily the method of choice except in special cases. For the most part cutaneous neoplasms are treated either with scalpel surgery or with electrosurgery. Most dermatologists treat the ordinary small epitheliomas with electrosurgery.

An ordinary basal-cell epithelioma 0.5 to 1 cm. in diameter and located in an area where there are no important underlying or adjacent structures will respond well to irradiation with various technics. I prefer applications of x-rays over a period of two weeks in divided doses up to a total of 4500 r instead of the single-dose method of 3000 to 5000 r. Conventional superficial x-rays with a half-value layer of approximately 0.75 mm. of aluminum are used. Ordinarily, seven treatments of 600 r each given every other day are sufficient. With larger lesions with a diameter of 2 cm. or more a smaller total dose of harder radiations suffices. Six treatments of approximately 600 r each, given every other day over a period of two weeks, constitute the technic I usually employ. The x-rays are filtered through 3 mm. of aluminum. The reaction from this quality of radiation may be quite pronounced.

In the treatment of primary squamous-cell epitheliomas of the skin of small size (less than 1 cm. in diameter) it is well to increase the total dose up to 5000 or 5500 r. To minimize the reaction this total dose can be given over a period of approximately three weeks — the so-called modified Coutard technic, which was very popular when it was first described but was supplanted by the single-dose intensive method. I have always liked the idea of protraction because it permitted me to give larger total doses with minimal cutaneous reactions.

Squamous-cell epitheliomas of the lips respond satisfactorily to radiation. However, the treatment of carcinoma of the tongue and other intraoral lesions, in my opinion, requires the combined talents of a surgeon and a radiologist. In some cases surgical excision alone is sufficient. In others the combination of interstitial radium and x-rays is necessary, and in extensive cases one requires a combination of x-rays, radium and surgery for successful results.

Conclusions

An attempt has been made to emphasize again that x-rays are still useful for the treatment of some diseases of the skin. Only a few diseases have been discussed to illustrate their usefulness. It would indeed be a step backward to accept the edict that x-rays are no longer useful in dermatologic practice. The modern dermatologist uses x-rays with greater skill, greater knowledge and greater accuracy than his forebears; he is much more discriminating, and he can predict better what the results of his treatment are going to be. The injuries from overirradiation are far less common than formerly.

To operate a dermatologic practice or a dermatologic clinic without the advantages of ionizing radiations and especially an x-ray machine would be denying patients the benefits to which they are entitled.

MESANTOIN IN THE TREATMENT OF EPILEPSY*

A Study of Its Effect on the Leukocyte Count in Seventy-Nine Cases

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BOSTON

IN 1950 we reviewed the literature on the serious side effects of anticonvulsants[1] and described 11 cases of cytopenia attributed to Mesantoin. Six of the patients treated had died. Since our review, 2 accounts[2, 3] of similar cases, as well as other relevant articles,[4-7] have appeared.

The article[1] referred to described general safeguards and advocated a routine supervision of blood counts that, it was hoped, would largely prevent such catastrophes. This routine, as we have followed it since then, entails a white-cell count and a differential count with a calculation of the number of neutrophils to be done at the following times: before the start of such medicine as Mesantoin;

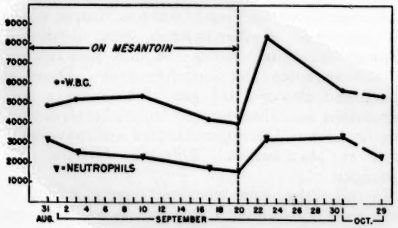

FIGURE 1. *Total White-Cell Count and Total Neutrophil Count in Case 1 during Mesantoin Therapy and after Cessation of the Drug.*

after two weeks on a reduced amount of the drug (partial dose); after another two weeks when full dosage is reached; monthly thereafter for the first year; and every three months from then on. Counts are done at least every two weeks if the number of neutrophils ranges between 2500 and 1600 per cubic millimeter. Medicine is stopped if the number drops to 1600 or less. In each case the physician's personal judgment determines the exact number of counts necessary to check errors, follow trends and establish levels.

A drop in the neutrophil count without a decrease in the total white-cell count is shown in Figure 1. In other cases, as in this, a first reduction in the total number of neutrophils may not be attended by a drop in the total white-cell count. For this reason we have stressed the number of neutrophils per cubic millimeter, which, of course, one can calculate by multiplying the total number of white cells per cubic millimeter by the percentage of neutrophils in the differential count. Mature and immature neutrophils ("band forms" and "stabs") are counted together. In the preparation of smears the one-cover-slip method is used.

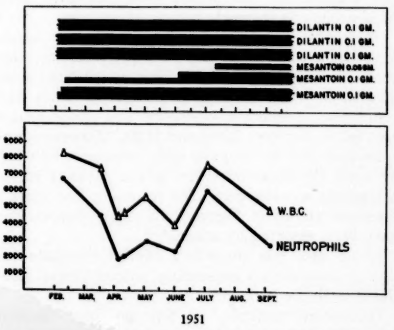

FIGURE 2. *Total White-Cell Count and Total Neutrophil Count in Case 2 during Gradual Increment of Mesantoin Medication over a Nine-Month Period.*

This paper reports hematologic findings in 79 patients whose blood counts were supervised in this way. The duration of Mesantoin therapy, at the time of the last counts, is shown in Table 1; 51 patients took the drug for over a year, and 13 for three to five years — an average of twenty-one months.

TABLE 1. *Duration of Mesantoin Therapy.*

DURATION OF LESS THAN 1 MO.	DURATION OF 1–6 MO.	DURATION OF 6 MO.–1 YR.	DURATION OF 1–3 YR.	DURATION OF 3–5 YR.
NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES
3	13	12	38	13

RESULTS

Eighteen, or 23 per cent, of the 79 patients had at least one neutrophil count below 2500 and were therefore supervised by more frequent counts

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Among these 18 patients there were only 2 (that is, 2.5 per cent of the 79) whose counts dropped to practical equivalents of the critical 1600. The count fell to 1640 in 1 of these (Fig. 1) and to 1560 in the other. There were no lower counts in the group.

Because of the low neutrophil counts Mesantoin was stopped in a total of 5 cases, including the 2 just mentioned. The other 3 patients had counts that dropped to between 2000 and 1600 and did not seem able to co-operate in the closer supervision of blood counts that we considered necessary for their protection at these levels. In all these cases the number of neutrophils rose promptly after Mesantoin was stopped.

It is possible, however, that these rises would have occurred even without the precautionary discontinuance of Mesantoin. This possibility is indicated by the fact that in 2 other patients who could give adequate co-operation and whose counts also fell to between 2000 and 1600, Mesantoin was continued and the drops in their cases were followed by rises like those observed in the patients whose Mesantoin was stopped. The counts in 1 of these 2 cases are shown in Figure 2. Similar observations have been reported by others.[6, 8]

In no case was there any clinical complaint or sign to indicate an impending serious illness associated with the leukopenia.

Individual patients, as pointed out, showed counts that dropped to or below the rather arbitrarily chosen precautionary values of 2500 and 1600 neutrophils per cubic millimeter. We were interested to learn whether or not, in contrast to these individual drops, there was for the whole group a downward trend in the neutrophil and total white-cell counts while the patients were taking Mesantoin. To get this information we averaged all the counts done before the start of Mesantoin therapy, all the counts done within two weeks of the start of therapy, all the counts done after the patient had taken the drug for a month, all done after two months, and so on at monthly intervals through all the counts done after the patients had taken Mesantoin for five years. These averages for neutrophil and total white-cell counts showed no trend downward or upward.

Data on 2 cases presented graphically in Figure 1 and 2 showed typical lowerings of counts to warning levels. In Case 1 (Fig. 1) the drug was withdrawn and the count rose. As pointed out above in the other case (Fig. 2) the neutrophil count rose again to normal values even though Mesantoin was not withdrawn.

Case Reports

Case 1. J. E. C. (M.G.H. 642724), a 16-year-old schoolgirl, began to have generalized seizures, usually in her sleep, with occasional incontinence and tongue biting. Neurologic examination 2 years later was not remarkable. Two electroencephalograms were mildly abnormal, with no localized or lateralized signs.

She was placed on Mesantoin, 0.1 gm. 4 times, and Dilantin, 0.1 gm. 4 times a day. The advisability of periodic blood counts on patients taking Mesantoin was first recognized after she had been taking the drug for 5 months. Counts begun at this time (August 31, 1949) are presented in Figure 1. They show a progressive decline in the number of neutrophils beginning at about the time at which serious drops of this sort have been reported as occurring in other cases. At first it was not reflected in the total white-cell count. It continued to a level of 1640 neutrophils per cubic millimeter, at which point Mesantoin was stopped, and the neutrophils rose to their initial levels, which they subsequently maintained (the last count was on March 24, 1952).

Case 2. R. P. N. (M.G.H. 390419), a 25-year-old woman, had had seizures since the age of 15, both "severe" (grand mal) and "mild" (petit mal). At the time of this report, the severe episodes were occurring about once a month, and the mild ones with an undetermined frequency. The electroencephalogram was grossly abnormal, with an abundance of high-voltage waves to as slow as 5 per second and without localized or lateralized abnormality. Other laboratory tests and neurologic examinations were normal.

A series of blood counts and the medicine taken are shown in Figure 2. The white-cell count dropped to a minimum of 4300 and the neutrophils to 1900; 1 week later, without change in medication, they rose to 4500 and 2300, respectively, and 1 month after that to 5500 and 3000. Subsequent neutrophil counts continued to stay above the precautionary values of 2500 and 1600.

Discussion

We did not find any correlation of drop in neutrophil counts with age, sex or amount of drug given. In age, most of the patients were distributed through the third, fourth and fifth decades; extremes were ten and sixty-five years. Doses of Mesantoin averaged 0.1 gm. three times a day. Mesantoin was always given in combination with one or more of the other standard anticonvulsants such as phenobarbital, Dilantin, Mebaral and bromides.

In this series, total white-cell counts of 7000 or more were never attended by total neutrophil counts of 2500 or less per cubic millimeter. In 41 counts done on a total of 19 patients showing 2500 neutrophils or less none demonstrated total white-cell counts over 7000 and only 2 counts of more than 6000. It therefore seems safe to omit the differential and neutrophil counts if the total counts are over 7000. One should realize, however, that errors can occur, and that the counts are often done by different technicians, some of whom may not be reliable. Hence the smear and differential count may be a vital check on such a laboratory error. We have noted that when the patient has received Mesantoin between five and eight months hints of white-cell depression may first occur; and therefore the middle of the first year is an important time to be on the alert. Our data again confirm the relative safety after one year on this drug. A drop from a total white-cell count of 6000 to one of 4000 may serve as a warning to watch the differential and neutrophil count carefully.

None of our 79 patients were clinically ill from this medication. Case 1 (Fig. 1), we believe, was protected from a possible blood dyscrasia complicating anticonvulsant therapy by Mesantoin. In all the patients there was at least one complete blood study, including platelet estimation, hemo-

globin measurement and red-cell count. These were repeated from time to time when indicated, particularly during the close scrutiny of patients whose white-cell counts were depressed. In this group of cases, however, no alteration in the red cells, hemoglobin or platelet estimation was found. No reasonable safeguard against unusual catastrophe is 100 per cent certain. It is always possible that a fulminating blood disturbance will occur a few weeks after the finding of a normal white-cell count. Fortunately, this has not been our experience, but the possibility must never be overlooked. Such disasters may be due to an error in a white-cell count or the addition to the patient's medication of some drug unknown to the doctor supervising the epilepsy, which either alone or in combination with Mesantoin has the dangerous results. Such a possibility should be kept in mind by an alert clinician, and the patients should be instructed to avoid medication without consulting the physician. They should instantly report any clinical signs that might uncover the possibility of such a complication.

It might be worth while in the future to arrange for bone-marrow punctures when a real depression of white cells is encountered. In the cases reported in this paper there were no clinical findings or complaints in the presence of the depressed white-cell counts. However, when any bleeding tendency occurs platelet counts and other blood studies are more urgent and the situation is more critical than when a benign leukopenia develops.

Summary and Conclusions

Effects of Mesantoin on the white-cell and neutrophil counts of 79 patients with epilepsy are described. The neutrophil counts of 23 per cent fell below 2500, and treatment was stopped on this account in 5 cases (6 per cent).

A planned supervision of white-cell and neutrophil counts amply justifies its trouble and expense. It is also evident that Mesantoin, when used under such supervision, is a relatively safe and efficient anticonvulsant drug.

We are indebted to Drs. Bernard M. Jacobson and Mandel E. Cohen for help with the hematologic and statistical data in this paper.

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MEDICAL PROGRESS

NUTRITION IN CLINICAL MEDICINE*

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NUTRITION in clinical medicine has come to have several different connotations depending on whether one is thinking of diagnosis and specific treatment or of patient management. Under the first heading have fallen the "classic" deficiency diseases such as scurvy, rickets, beriberi and pellagra. Indeed, in the minds of many physicians the subject of nutrition has remained identified with these deficiency states, disorders rarely encountered in the United States and today readily treated.

On the other hand, the part played by nutrition in patient management has often been neglected, particularly since, in the past, nutritional status was difficult to appraise and also less frequently was thought to be the determining factor in the prognosis of the patient. Now that problems relating to infection are more readily controlled, the importance of supportive care is beginning to receive general recognition; however, the principles of nutrition that should guide such treatment are less widely understood. One of the purposes of this review is to discuss some of the more recently evolved concepts of nutrition as they apply to the management of nutritional problems in patients. Yet it should be stressed that the interests of nutrition in the patient extend beyond considerations of supportive care and the treatment of various deficiencies. In the field of preventive nutrition, for example, research activities are constantly directed to finding ways of preventing atherosclerosis, cancer, obesity and a variety of metabolic disorders. In the field of diagnostic nutrition a number of recently developed technics involving use of iso-

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topes and other tracers are being successfully applied in the precise measurement of body constituents and hence determination of the nutritional status of patients.

It is not possible to cover the whole field of contemporary nutrition in its complex relation to medicine. Discussion of such important subjects as kwashiorkor, the role of diet in the genesis and treatment of atherosclerosis, the part played by salt restriction in the treatment of hypertension and edematous states, and the diet in liver disease has been omitted since these subjects have been thoroughly and repeatedly reviewed elsewhere. Accordingly, this review attempts only to outline a few representative but less well known aspects of nutrition as they relate to important clinical problems.

Nutrition in Supportive Care

General Considerations

A major objective in feeding patients is to replenish or maintain protein stores. However, to ensure that optimal protein utilization will take place in a given patient is a complex and often difficult problem. A number of nutritional studies in the recent past have been concerned with the various factors that influence protein utilization, of which the following are selected as being of particular clinical importance: carbohydrate intake; fat intake; protein and caloric intakes, and ratios of calorie-nitrogen intake; state of protein reserves; rate, timing and route of administration of protein and calories; potassium intake; and trauma, infection and "toxic" factors.

It is not possible to list these items in order of importance since any one of them may be a limiting factor, depending on the clinical circumstances. Indeed, Peters[1] recently offered a reminder that it is the interrelations of foodstuffs in metabolism that help make their individual roles intelligible. Accordingly, these modifying factors should be considered in relation to one another, not as isolated phenomena.

Carbohydrate Intake

In total starvation, protein reserves are called upon to meet the body's irreducible glucose requirement, and also to make up the difference between energy requirements and the energy actually supplied from fat stores. Gamble[2] and his associates demonstrated in normal volunteer subjects the virtues of consuming small amounts of glucose (100 gm. per day) during a period of what otherwise would have been total starvation. This small glucose intake alone diminished protein losses by 50 per cent, with a corresponding saving of intracellular constituents. Symptoms of ketosis also were relieved or prevented by this amount of glucose, and losses of sodium and water from the extracellular fluid were reduced by half.

Carbohydrate is the major fuel of the central nervous system.[3] Fat cannot be converted to carbohydrate in appreciable amounts; moreover, carbohydrate is needed to "prime" the machinery of the Krebs cycle, which acts as a common oxidative pathway of all foodstuffs.[1] In addition, Geiger[4] has postulated that simultaneously fed carbohydrate may promote protein synthesis by providing precursors for the synthesis of nonessential amino acids. These acids must be available when new protein is being manufactured.

Thus, a deficiency of carbohydrate, if it occurs, must be made good from body stores of protein, and in disease the body can ill afford to waste such stores. By contrast, a deficiency of calories in the diet can be partly made good from depot fat; thus, it may be seen that an energy deficit is usually a less serious matter than a carbohydrate deficit.

Fat Intake

Swanson[5] has shown that dietary fat may play a part in protein metabolism beyond its role as a nonspecific source of calories. In rats at low levels of caloric intake (25 per cent of requirements), an increase in the fat content of protein-free diets from 10 to 20 per cent was associated with a remarkable decrease in protein breakdown although the total caloric intake had not been altered. Earlier, other investigators[6, 7] had demonstrated that even a small amount of fat in the diet of rats is associated with better utilization of the diet as a whole.

Caloric Intake

It is obvious that the energy requirements of the body must be met at all costs. Adaptation to undernutrition by means of decreased activity and a lowered basal metabolic rate occurs in time, but the ability of the body to adjust itself in this way to a decreased food intake is at best limited, particularly during illness or after injury when acute caloric deprivation occurs in the presence of increased energy requirements.[8] Under such conditions the major burden for supplying calories necessarily falls upon the fat depots. This is strikingly shown by Moore and his associates,[9] who have demonstrated by means of deuterium dilution studies that in the early postoperative period fat appears to be burned at a rate of 200 to 400 gm. per day, or 1800 to 3600 calories in a twenty-four-hour period. Later in convalescence, this rate of fat oxidation more closely approximates that seen during semistarvation.

Unfortunately, body fat cannot of itself meet all the energy demands of the organism. Even if the requirement for essential carbohydrate is met and enough protein is given to replace (in theory) that lost as a result of "wear and tear," the previously well nourished subject will remain in protein deficit if his diet does not at the same time provide an adequate supply of calories.[10] Dietary fat is more

available for this purpose than body fat and will correct this deficit.[11]

Thus, when protein stores are not excessively depleted and when "essential" carbohydrate and "replacement" protein are given, the caloric intake is the important determining factor in protein utilization.[12] Under such circumstances, an intake high in calories should favor optimal utilization of dietary protein.

Protein Stores

The influence of caloric intake on protein utilization tends to wane as the patient becomes increasingly depleted.[13] Swanson[5] has demonstrated in protein-starved rats that the caloric intake must fall to approximately 25 per cent of requirements before appreciable additional amounts of endogenous protein are broken down to meet energy needs. Under these arduous circumstances such protein as is still potentially available is retained with increasing tenacity until fat stores become exhausted.

Depleted patients also show lack of sensitivity, in terms of protein breakdown, to shifts in caloric intake when their intake of protein remains low. Therefore, it is manifestly desirable to stress protein in the diet of the depleted person since utilization and storage of protein can be increased only by an increase in protein intake. Calories should also be given to such patients in liberal amounts when possible, but here provision of calories may be less crucial than provision of protein and, of course, essential glucose.

Cox and his associates[14] performed studies on young rats to determine to what extent ingested protein can be used for tissue growth when insufficient calories are fed. They found that the rate of growth in protein-depleted animals continued to diminish as the caloric intake was progressively reduced. At 25 per cent of ad libitum intake growth ceased, and the animals only maintained weight. Cessation of growth took place even if a considerable quantity of protein was present in the subcaloric diet. At the low levels of caloric intake, however, the animals that received their calories as a dextrose-hydrolysate mixture weighed significantly more at the end of the experimental period than the animals that ingested dextrose alone. When stock animals with no pre-existing nutritional deficiency were subjected to caloric deprivation growth ceased on restriction of caloric intake to 50 per cent of ad libitum intake. At 26 to 37 per cent of caloric "requirements" no appreciable advantage was observed when dextrose and a mixture of dextrose and protein hydrolysate were compared from the standpoint of their influence on growth. In experimentally traumatized animals restricted to a caloric intake of 50 per cent of requirements, weight was maintained better with a dextrose-hydrolysate mixture than with dextrose alone. Lastly, when weight changes of protein-depleted animals were followed with the animals on various mixtures of protein and carbohydrate, all providing the same number of calories (approximately 50 per cent of requirements), a protein-carbohydrate ratio of 1:4 gave the best results. In other words the largest weight gain was achieved with 20 per cent of the total calories in the form of protein hydrolysate. Higher proportions of protein hydrolysate resulted in a progressively lower rate of weight gain.

Between depleted protein stores at one extreme and intact protein stores at the other there is a middle ground where dietary calories may retain much of their favorable influence on protein utilization.[12] Yet when food intake is limited to less than optimal quantities it is reasonable to decrease the ratio of calorie-protein intake so that an increasingly larger fraction of the diet consists of protein.

Rate, Timing and Route of Administration of Nutrients

The rate at which the body can utilize amino acids presented via the portal circulation or via the systemic circulation is still not well defined. Geiger[4] has pointed out that simultaneous fat intake may improve utilization of orally administered protein. In his view this particular protein-sparing action of dietary fat may take place by virtue of the retarding effect the fat has on the rate of amino acid supply from the digestive tract. This explanation requires the assumption that the rate at which amino acids can be taken up from the circulation for protein synthesis is strictly limited. Earlier work[15] on the utilization of parenterally administered amino acids (and small polypeptides) appears to provide some support for the admonition that amino acids should not be presented to the circulation too rapidly, either from the intestinal tract or through intravenous injection. However, Davidson and Eckhardt[16] administered an acid hydrolysate of casein supplemented with tryptophane and glycine intravenously to 2 normal subjects and 5 patients with varying degrees of liver impairment. The preparation contained no peptides and was essentially free of dicarboxylic amino acids. The rates of infusion varied widely, but no correlation could be found between the infusion rate and the quantity of nitrogen excreted in the twenty-four-hour urine, either in individual patients or from patient to patient. The authors concluded that the rapid rates of infusion did not increase either the urinary output of amino acids or the rate of deamination.

Recently, Elman[17] reported nitrogen-balance studies in patients given infusions of an inadequate caloric mixture of glucose and amino acids. The findings indicated a greater utilization of the amino acids when glucose was infused at the same time, and when the mixture was infused at a slower rate.

Human serum albumin[18-20] and also modified human globin[21-23] and packed human erythrocytes[24] have been employed on an experimental basis as potential protein sources that can be administered intravenously. Janeway[20] has stated that "the role of serum albumin in the total protein economy of the body, its intermediary metabolism, and its relation to the formation of such tissues as bone matrix are incompletely understood." Probably by raising serum albumin levels in hypoproteinemic states, parenterally administered albumin to some extent spares dietary and body protein for other uses. Since parenterally given albumin is broken down only slowly in the body, its usefulness as a source of amino acids is necessarily limited. There is some evidence[19] that in protein-depleted patients a large portion of intravenously administered albumin ultimately may be used in the manufacture of tissue protein. However, despite the potential value of albumin in certain nutritional problems, its inordinate cost makes widespread use impractical.

Modified human globin has been administered intravenously to patients by a number of groups of investigators.[20] Apparently, intravenously given globin will maintain a positive nitrogen balance in an undernourished person, even when the globin is the sole source of nitrogen. There is evidence that globin so given is rapidly broken down to polypeptides and amino acids and that these products in turn are resynthesized into tissue and serum proteins.[21, 22]

Unfortunately, globin appears promptly in the urine in large amounts soon after it is administered. Twenty-five per cent or more of the amount given may be lost in this way in a twenty-four-hour period.[22] Moreover, Plough and his associates[23] found that single rapid infusions of modified human globin tested for use as a plasma substitute were associated with a high incidence of toxic reactions such as erythema, pruritus, urticaria and fever. The patients so studied also displayed an increase in red cells, white cells and casts in the urine. In 1 patient studied by balance methods, only a fourth of the administered globin was retained in the body, and it was believed that this material was not metabolized but stored unchanged. Thus, at present, it appears that opinion of the clinical value of globin must be reserved.

Calloway and Mowrey[24] have reported preliminary studies on erythrocytes as a source of protein for parenteral use presenting evidence that a number of hypoproteinemic patients given large quantities of packed red cells were able to break down the erythrocytes and use the protein portion in the synthesis of serum albumin and tissue protein. Unfortunately, injection of red-cell suspensions is followed in a significant number of cases by viral hepatitis. Moreover, there is always the likelihood that abnormal amounts of iron pigment will accumulate in the body as a consequence of repeated red-cell infusions.

By means of dextrose and protein hydrolysates given by vein it is possible to fill the body's needs for carbohydrate per se and for protein. However, it has never been practicable to meet energy requirements for prolonged periods solely by parenteral administration of glucose.[1] To avoid excessive glycosuria it has been found desirable to limit the rate of administration of dextrose solutions to approximately 0.4 to 0.7 gm. per kilogram of body weight per hour.[25] In concentrations exceeding 5 per cent glucose solutions are damaging to veins, roughly in direct proportion to their hypertonicity. Therefore, it is ordinarily necessary to administer glucose in a dilute solution along with volumes of fluid that may, under certain circumstances, be dangerous to the patient.

For these reasons there has been a need for a nonsclerosing preparation for intravenous administration that contains a large supply of calories in a small volume of fluid. Fat emulsions[26, 27] appear to offer a solution to this problem. Such preparations contain fat particles averaging less than 1 micron in diameter, and a 15 per cent fat emulsion with 4 per cent glucose provides 1600 calories per liter. Fat particles do not exert an osmotic effect; accordingly, fat may be injected in high concentrations without damage to veins and in a relatively small fluid volume. Unlike glucose (dextrose) and amino acids, fat is not excreted in the urine in significant amounts.

In several laboratories[28-31] it has been possible to prepare fat emulsions suitable for intravenous use in patients. However, difficulties in manufacture, storage and transport of these fat preparations have seriously restricted clinical use of the material. The commonest untoward effect has been a febrile response to the fat.[32] The cause of pyrogenicity in fat emulsions is not well understood. Stability of such emulsions in the presence of changes in environmental temperature and rough handling also presents a formidable problem. Creditor[33] has shown that the mechanical fragility of red cells may be increased while the cells are actually in contact with plasma that is lipemic because of added fat emulsion. However, such changes do not persist after the lipemia has cleared.[34]

Johnson, Freeman and Meyer[31] reported that thrombocytopenia developed in 3 patients who received multiple infusions of a 20 per cent olive-oil emulsion containing 1 per cent lecithin as the emulsifying agent. Stare et al.[35] did not observe toxic effects of this nature in 500 patients who received a total of more than 1000 infusions of fat; the incidence of all types of reactions, including mild ones, was 12.7 per cent.

Despite the difficulties inherent in obtaining consistently nonpyrogenic and uniformly stable fat preparations, a number of investigators have re-

ported favorable results in patients after the intravenous use of fat emulsion as a caloric supplement.[31, 34] Therefore, it is to be regretted that a considerable gap still exists between preparations that can be produced under laboratory conditions and administered on an investigative basis and preparations that can be manufactured and distributed in quantity and have a long "shelf life."

The limitations of glucose as a source of calories by the intravenous route also have led to use of a mixture of glucose and fructose (invert sugar) in intravenous therapy. Weinstein[36, 37] reported that invert sugar could be given to patients at a rate of 1.5 gm. per kilogram of body weight per hour (twice or thrice the tolerance rate of glucose alone) without appreciable loss of the infused hexoses in the urine. However, later studies by Smith, Beal and Frost[38] failed to disclose any advantage of invert sugar over glucose so far as renal tolerance was concerned.

Tolerance to fructose administered intravenously alone has also been under investigation. Weichselbaum, Elman and Lund[39] administered a liter of 10 per cent glucose and 10 per cent fructose in water, respectively, by vein on separate days to each of 10 human subjects and found that fructose given at rates up to 2.0 gm. per kilogram of body weight per hour was better retained in the body than an equal amount of glucose given considerably more slowly. These findings have been confirmed by Bertino et al.[40] However, other reports by Miller and his associates,[41] Smith, Ettinger, Seligson and Lightcap[42] and Beal and his co-workers[43] all indicate that glucose and fructose are roughly equivalent from the standpoint of urinary wastage. Beal et al.[43] discovered that significant quantities of reducing sugars often were still present in the urine four and five hours after completion of the injection. They pointed out that earlier studies attesting to the superiority of fructose-containing solutions were based on procedures in which urine was collected not more than three hours after cessation of the infusion. These differences in duration of collection period may account for some of the discrepancies found in the various published reports on the subject. Rates of administration of the various sugar preparations have varied widely from study to study; this has also made interpretation of the results difficult.

Although carbohydrate and amino acid preparations can usually be given safely by the intravenous route, grave doubts have been raised concerning the safety of administering such preparations by hypodermoclysis.[44, 45] Abbott and his associates[46] have shown that the subcutaneous, intramuscular or intraperitoneal administration of preparations containing sugar or amino acid may produce a transient decrease in blood volume of 20 per cent or more, with a corresponding rise in hematocrit and depletion of plasma electrolytes. These changes are not infrequently accompanied by the signs and symptoms of shock.

Since glucose displays a relatively slow rate of diffusion through interstitial spaces and across vascular membranes an isotonic dextrose solution administered by hypodermoclysis tends to attract extracellular fluid and electrolytes to the injection site. An additional loss of plasma and interstitial fluid might be expected to occur because of an intracellular shift of water resulting from the hypotonicity of the extracellular fluid. When a hypertonic solution is given by hypodermoclysis all these changes occur to a much greater extent. Abbott and his co-workers[46] point out that the rate of absorption of a solution depends on the similarity of its composition to interstitial fluid, its tonicity, the molecular size of the solutes and also the extent of the surface area of the fluid in contact with the absorbing membrane. Since hyaluronidase causes subcutaneously administered solutions to diffuse over a greater area and increase the rate at which fluid can be administered it may well intensify the undesirable effects of a hypodermoclysis. Therefore, the administration of large volumes of fluids containing sugar or amino acid by hypodermoclysis, with or without hyaluronidase, is likely to be a dangerous procedure unless the fluids are given in small quantities intermittently, or very slowly. Administration by hypodermoclysis of isotonic solutions containing little or no inorganic electrolytes, or of hypertonic solutions, is certainly contraindicated in patients who are dehydrated, salt deficient or hypotensive.

Potassium Intake

Because of the high content of potassium in muscle, it has been hypothesized that this cation is also necessary for synthesis of muscle protein. Cannon, Frazier and Hughes[47] have pointed out that under favorable conditions of nutritional rehabilitation a good diet would furnish both nitrogen and potassium. If a patient is unable to eat well and must be fed parenterally, it is customary to attempt to provide carbohydrate, calories, amino acids and vitamins, and yet little provision is usually made to supply intracellular electrolytes as well. Cannon and his associates have reported studies indicating that the efficiency of parenteral alimentation might be considerably improved by supplementation with potassium salts. In confirmation of earlier work[48, 49] they found in protein-depleted rats that a repletion ration affording an adequate supply of calories, vitamins, amino acids and salts was well accepted and caused effective recovery of lost weight. By contrast removal of potassium from the salt mixture in the ration led to poor food consumption, failure to gain weight adequately, cardiac lesions and death. Addition of small amounts of potassium chloride to the deficient ration enabled the animals quickly to achieve effective protein

repletion. Cannon et al.[80] believe that the manifestations of potassium deficiency may become more severe as the intake of sodium chloride increases. On the other hand when intake of sodium chloride is lowered the effects of potassium deficiency may become correspondingly less severe.

Whitney and Bennett[81] have demonstrated that a diet high in potassium chloride will suppress the catabolic effect of ACTH. A control group of rats studied displayed a significant increase in urinary nitrogen during ACTH administration; by contrast, animals given supplementary potassium chloride showed virtually no increase in nitrogen excretion when the same amount of hormone was given.

Eliel, Pearson and White[82] have shown that patients deprived of potassium and phosphate in the postoperative period display more pronounced losses of nitrogen than those given optimal amounts of these elements under otherwise similar conditions. However, studies on the role of potassium in protein utilization in human subjects have been infrequent, and further work in this important field is needed at the clinical level.

Trauma and Infection

Utilization of protein during surgical convalescence depends to a large extent on the "phase" through which the patient is passing. Moore[83] has summarized the "normal" sequence of metabolic events in surgical convalescence under four headings: the adrenergic-corticoid phase, the corticoid-withdrawal phase, the spontaneous anabolic phase and the fat-gain phase. Such headings were chosen as being descriptive of the usual clinical and metabolic picture after operation. The first phase lasts approximately five days (depending on the magnitude of the surgical procedure), during which a marked nitrogen deficit frequently exceeds what might be expected in simple starvation. The mechanism of this nitrogen catabolic response is not well understood. However, it is now recognized[84] that such a response cannot be wholly explained as a simple matter of adrenocortical overactivity due to stress and superimposed on starvation and immobilization. Whether protein utilization can take place during this phase is largely an academic question since there is usually no nitrogen intake during this period. Indeed, it remains to be proved that the parenteral administration of amino acids during the early postoperative period is a desirable procedure.

The corticoid-withdrawal phase typically occurs toward the end of the first postoperative week, and during this phase losses of such body constituents as protein and fat are sharply reduced. By the ninth postoperative day intake of nutrients may approach normal, and it is at this time that the anabolic phase begins. Lean body tissue is replenished, and the patient regains strength and vigor. There is no controversy about the importance of an adequate intake of protein and calories during this phase. In the experience of Moore and Ball[85] protein anabolism during surgical convalescence requires a high caloric intake with ratios of calorie-nitrogen intake of 150 or higher.

Therapeutic Nutrition

Celiac Disease

Several years ago Dicke,[86] of the Netherlands, observed that patients with the celiac syndrome appeared to react particularly unfavorably to wheat (and rye) flour in the diet. To test this observation Weijers and van de Kamer[87] performed careful studies on the role of wheat in the diet of celiac patients. Their findings were dramatic. They observed that whenever the diet of such patients contained wheat, even in very small quantities, the patients became pale, appetite disappeared, weight was lost, and diarrhea and steatorrhea increased. As soon as all wheat flour was left out of the diet the unfavorable symptoms became less marked or disappeared entirely, and the general condition of the child improved. Similar findings were reported in 30 consecutive cases of celiac disease, and these results have more recently been confirmed by investigators in England.[88]

Van de Kamer and Weijers[89] demonstrated a close correlation between the harmful effect of wheat flour and the amount of fat excreted per day in the feces. They were unable to confirm the finding of earlier investigators that starch is the harmful substance for celiac patients. On the contrary their preliminary experiments indicated that the source of the trouble lay in the protein fraction of wheat, the wheat gluten, in which the gliadin seemed to be especially implicated. Accordingly, the Netherlands investigators concluded that the beneficial effects of the banana diet recommended by Haas[90] and of the fruit-vegetable diet may be explained by their dearth of wheat.

The Dutch workers went on to analyze the feces of celiac children for their content of saturated and unsaturated fatty acids. In about 20 patients with celiac disease, it was shown that the absorption of unsaturated fatty acids was always notably better than that of saturated fatty acids. When oils with a relatively high content of unsaturated fatty acids were given to celiac patients their "coefficient of fat absorption" became normal. From these findings and others it appears that for the diet of celiac patients olive oil, soybean oil and other unsaturated edible oils are to be preferred to butter, beef fat and such saturated oils as coconut oil. However, it seems clear from the work of Weijers and his co-workers that the harmful influence of wheat gluten in such patients cannot be nullified by concurrent incorporation into the diet of an unsaturated oil as the only source of fat. Actually, the Dutch investigators believe that in

patients with celiac disease wheat gluten (or rye) precipitates rather than causes a disturbance in fat metabolism, thereby bringing into clinical evidence a disease already latent and probably congenital in origin.

Uremia

Kolff[61] has reported on the use of a "forced" high-calorie, low-protein diet (Borst regimen) in the management of uremic states. He has shown that with a few exceptions such a regimen effectively suppresses endogenous protein breakdown in patients with acute and chronic renal disease and in volunteer subjects with normal kidney function. Uremic patients who faithfully follow such diets feel better and seem to improve their chances of surviving uremic exacerbations. A typical daily diet of 200 gm. of butter and 200 gm. of sugar (2500 calories) was taken by a normal volunteer subject for twenty-seven days. Twenty-four-hour urea excretion was reduced to 5 gm. by the tenth day; after twenty days it was less than 2.5 gm.

The major problem in the use of a diet such as the one recommended by Kolff, of course, is the difficulty of persuading the nauseated, uremic patient to take it. Kolff has suggested the use of frozen butter pills filled with sugar and has also found an emulsion of butter, sugar and a little flour, flavored with coffee extract, to be acceptable by the anorexic, uremic patient. Oral fat emulsions[62] also have a useful place in the nutritional management of such patients. It appears, however, that final success in the dietary therapy of uremia frequently depends on the energy and persistence of the physician in charge of the case.

Diabetes Mellitus

Johnson and Rynearson[63] have described an unusual follow-up study of a diabetic patient who was first seen in 1921 at the age of thirty-two and who presented himself for re-examination at the age of sixty-one. From 1922 until 1950 this patient had adhered faithfully to a daily diet of 2750 calories, of which the constituents were 46 gm. of carbohydrate, 50 gm. of protein and not less than 254 gm. of fat. Moreover, he had consistently boiled all vegetables for fifteen minutes and had drained and discarded the water. No vitamin pills had been taken at any time. He observed a weekly fast period of half a day, and the only change in the regimen during the twenty-nine years involved an increase in his daily protamine zinc insulin dosage from 30 to 45 units.

On re-examination in 1950 it was found that he had gained 15 pounds in weight. His blood pressure was normal. Funduscopic and neurologic examinations disclosed normal findings. Normal values were obtained for cholesterol, cholesterol esters, phospholipids, fatty acids and total lipids in the blood. The only evidence of arteriosclerosis was calcification along both femoral arteries disclosed by x-ray examination. There was no indication of vitamin deficiency. The diabetes was slightly out of control, with glycosuria and fasting blood sugars ranging between 158 and 188 mg. per 100 cc.

In view of the present controversy over the possible dangers of a high-fat diet, it is of special interest that in such a well documented case an extraordinarily high-fat intake of twenty-nine years' duration has been shown to be well tolerated by a diabetic patient, and not associated with undue degenerative vascular disease.

The potential value of fructose in the treatment of certain diabetic states has been under renewed discussion since fructose-containing solutions for intravenous administration have become commercially available. Oral use of fructose in diabetes was abandoned many years ago when it was learned that the administered fructose was converted to glucose with increasing efficiency in the process of intestinal absorption.[64] However, since fructose can be phosphorylated through a hexokinase system distinct from that involved in glucose phosphorylation,[65] utilization of it once it gets into the circulation appears to be largely independent of influence from hormones such as insulin, which ordinarily regulate the rate of passage of glucose into cells.

Miller et al.[41] studied the "utilization" of intravenously given fructose in patients with diabetes mellitus. They found that the fructose was well utilized as judged by fructose tolerance curves, changes in serum inorganic phosphate levels and rises in blood levels of carbohydrate intermediaries after fructose injection. Also, Chernick and Chaikoff[65] reported that the livers from alloxan-diabetic rats were able to oxidize C^{14}-labeled fructose at a normal rate whereas conversion of C^{14}-labeled glucose to C^{14}-labeled carbon dioxide under similar conditions was greatly inhibited.

Detailed studies on the metabolism of intravenously given fructose by patients with impaired glucose tolerance from diabetes mellitus or parenchymal hepatic disease have been reported by Smith, Ettinger, Seligson and Lightcap.[42] These authors found that the rate of disappearance of fructose from the blood has the characteristics of a first-order reaction and that its rate of utilization appears to be directly proportional to its concentration in the blood. Although the rates of fructose disappearance were measurably prolonged in patients with acute hepatitis, Laënnec's cirrhosis and diabetes, impairment of fructose tolerance was relatively slight and not at all comparable to impairment in tolerance of the same patients to glucose.

When responses of serum inorganic phosphate to glucose and fructose respectively were compared it was noted that the phosphate levels fell more rapidly after fructose administration and also returned more rapidly to normal. Much higher levels

of such carbohydrate intermediaries as pyruvate, lactate and alpha-ketoglutarate were found in the blood after fructose administration than could be measured after glucose administration. For this reason the authors suggested that a *qualitative* difference in the metabolic pathways of fructose and glucose may exist.

Since glucose utilization is temporarily inhibited after a prolonged fast ("starvation diabetes") attempts have been made to discover whether utilization of fructose would be similarly impaired under conditions of starvation. Wyshak and Chaikoff[66] compared the relative abilities of liver slices from normal and fasted rats to metabolize radioactive glucose and fructose. It was determined that the ability of livers from rats fasted seventy-two hours to convert glucose to carbon dioxide decreased by about 50 per cent; however, livers from rats fasted under similar conditions showed no significant decrease in ability to oxidize fructose. Despite the difference in oxidation of the two sugars, it was of interest that virtually no lipogenesis from either of the added substrates took place at the end of the seventy-two-hour fast. Hepatic glycogenesis from C^{14}-labeled glucose was markedly impaired by a forty-eight-hour fast. However, it was learned that conversion of C^{14}-labeled fructose to glycogen was about the same in control and fasted livers.

Body Fat, Obesity and Regulation of Food Intake

One of the difficulties in evaluating the state of nutrition has been in measuring body fat content. This problem has attracted increasing attention in recent years, particularly in connection with the problem of obesity. Brozek and Keys[67] have written a comprehensive review of this subject. Direct analyses of body fat have been exceptional, the only modern available data being those of Mitchell et al.[68] and Widdowson, McCance and Spray.[69] Indirect estimates have been based on four approaches: anthropometric data; body density; total body water; and fat-soluble indicators.

Workers who have had personal experience in the determinations of the fat content of man or laboratory animals are in general agreement that body weight, even when corrected for skeletal size, is a poor indicator of fatness. First of all, most of the actuarial tables on which the concepts of "standard," "ideal" or "desirable" weights are based were obtained in persons wearing shoes and ordinary clothing. No reliable data are available to permit a correction to nude weight, even on a collective basis. For application to individual cases, the size of the subject, season of the year and regional customs have to be taken into account. Variations in skeletal framework are almost impossible to evaluate without x-ray determinations. The concept of "ideal" or "desirable" weight is based solely on actuarial studies of longevity. With the application of such considerations as physical attractiveness, productive capacity and many others, as many answers can be obtained as there are criteria.

A refinement of the method of estimating body fat in terms of height-weight relation involves consideration of fat-fold thickness. The subcutaneous tissue contains a large fraction of the total fat depot in man. Skin-fold measurements are thus an index of body fat content.[70] Calipers used in this procedure by Richer[71] have been improved by the addition of a device that automatically determines the pressure at which the measurements are made. The method can be further standardized by avoidance of extremes of temperature[72] and by measurements made at the proper sites. Roentgenograms, used by Stuart and Sobel[73] and Reynolds and Asakawa[74] make it possible to obtain a reliable picture of the thickness of subcutaneous fat layers. By means of either technic a partition of the fat-skeleton-muscle mass can be calculated.[75]

Body-density methods are based on the fact that, per unit volume, fat is considerably lighter than other body constituents. Subjects are weighed under water according to Archimedes's principle, and their specific gravity determined. From these data "lean body mass" and total body fat are calculated. Corrections for air in the lungs and in the gastrointestinal tract have to be taken into consideration in these determinations.

A number of substances have been tested for their adaptability as "dilutes" in total body water. To be acceptable for use in determination of total body water (TBW) such substances must, according to Brozek and Keys,[67] satisfy five criteria: they should rapidly dissolve in all the water of the body, not be concentrated or selectively destroyed by certain parts of the body, be eliminated at a measurable rate, not be toxic in the amounts needed and be readily measurable in the serum. Heavy water and antipyrine appear to be the most satisfactory substances so far studied; however, thiourea, sulfanilamide and tritium-labeled water have also been used in man for this purpose, with fairly good results. All these methods have certain limitations. First of all, comparisons with absolute (chemical) determinations of body fat are necessarily rare. Secondly, some of the substances usually show some degree of localized concentration or, like deuterium and tritium, exchange with organic hydrogen. Lastly, the degree of hydration of the body may vary from one normal person to another and, also, within the same person with time.[10] For this reason McCance and Widdowson[76] have suggested separate consideration of the intracellular and extracellular compartments, the thiocyanate or inulin spaces being used as indexes of extracellular water. From such studies[77] it has been shown in the normal person that approximately 70 per cent of body water is in cells. "Extracellular fluid" varies between 15 and 25 per cent of body weight,

depending on the method used. Bone mineral makes up between 5 and 9 per cent of body weight. The various uncertainties inherent in many of these measurements have been discussed by Brozek and Keys.[67]

Behnke[78] has used dissolved nitrogen as a fat solute for the estimation of total body fat in man. In laboratory animals, cyclopropane has also been employed.[79] Although these methods are not yet technically satisfactory they point to the possibility of an independent and more direct approach to the measurement of the "adipose compartment."

As a result of studies of body composition, the commonly accepted interpretation of the basal metabolic rate as it is ordinarily calculated has been modified. It has been shown, for example, that an important difference in body composition exists between males and females. This difference is already well established at puberty, females having a consistently higher content of fat in proportion to body weight than males.[80] When basal metabolic rates are correlated with lean body mass rather than body weight or surface area it is found that the metabolic rates per unit of lean body mass are identical for the two sexes.[81] Age is also an important variable. Body fat content increases with age, even when body weight remains constant. Here, again, if the basal metabolic rate is expressed in terms of lean body mass, a much more constant value is obtained than when body surface is used as the correlative.[82] Obviously, body surface cannot accurately reflect a relative increase in body fat.

An existence involving constant physical exertion over a long period was found by Keys[81] and his associates to be associated with a body weight greater than normal but with a less than normal content of fat. The "lean body mass" of a group of physically active men was shown to be greater than that of their age and height controls, with no trace of the "disuse atrophy" of muscle that is commonly thought of as being characteristic of the aging process.[67] Welham and Behnke[83] had previously shown that "overweight" professional athletes have a higher than "normal" specific gravity and hence a higher than normal proportion of lean body mass and a proportionately low fat content. This example has been used to demonstrate the inadequacy of body weight per se as a measure of obesity. Conversely, in obesity, the increase in lean body mass is small in comparison with total weight increase. When basal metabolic rates are calculated on the basis of lean body mass, it is learned that during the period of "active" accumulation of fat, basal metabolic rates are high. During the period of "static" obesity oxygen consumption per unit of lean body mass again is normal.[67]

Statistics of the Metropolitan Life Insurance Company[84] have shown that in its insured population the mortality between ages twenty and sixty-four is 50 per cent higher among overweight persons than among those of normal weight. The mortality from cardiovascular and renal diseases is increased by more than 50 per cent, and that from hepatic disease by more than 100 per cent.

Treatment and prevention of obesity have been hampered by lack of understanding of its etiology. To be sure, obesity can develop only if there is a prolonged imbalance between energy intake and output. This statement, however, is descriptive rather than explanatory. The problem is to determine why the mechanism (or mechanisms) that regulates food intake has been altered in such a way that energy intake chronically exceeds energy expenditure. To understand the causes of such an imbalance, the normal mechanism of food intake must be understood. Physiologic knowledge concerning this important mechanism is sketchy. In recent years, a "glucostatic" theory based on experimental studies on human subjects and animals of various species has been proposed.[85-87] This theory, which has yet to be independently confirmed, has been described in detail in a previous review.[88] Briefly, it postulates that the rate of glucose utilization by two symmetrical hypothalamic centers (feeding centers) is an important element in the regulation of food intake. Decreased levels of blood glucose (hypoglycemia) or decreased rates of utilization of blood glucose (metabolic hypoglycemia) increase food intake. Because of the role of "effective" blood glucose in determining the rate of fat utilization[89] and of gluconeogenesis from protein[90] such a glucostatic mechanism for the regulation of the urge for food seems to fit in well with other relevant regulatory mechanisms. Moreover, the glucostatic theory makes it possible to predict that disturbances in carbohydrate metabolism and also in fat and protein metabolism may influence food intake, causing either polyphagia or anorexia.

Obesity can be due to genetic, traumatic or environmental factors.[91] The mode of action of genetic factors has been studied in detail in the "obesity-hyperglycemia" syndrome of mice, a mendelian recessive condition characterized by extreme obesity, hypercholesterolemia and an insulin-resistant hyperglycemia. Pair-fed obese and nonobese animals given the same amount of radioacetate handle it in profoundly different ways. The obese animals incorporate a much higher proportion of the administered labeled compound into fatty acids and cholesterol than the nonobese controls. Hormonal studies have shown that the obese, hyperglycemic mice hypersecrete two pancreatic hormones, insulin and another substance with hyperglycemic and anti-insulin properties. Although the effect of insulin on blood glucose in these animals is more than neutralized by that of the other factor (which presumably is the first to be hypersecreted) its effect on lipogenesis seems to be unopposed and may be

responsible for the increase in fat synthesis from acetate.

"Traumatic" obesity has possible counterparts in the variety of experimental obesity induced by gold thioglucose[92] and in obesity that follows the placing of electrolytic lesions in the area of the ventromedial nuclei of the hypothalamus.[93] The role of environmental factors in the etiology of obesity is illustrated by studies on the significance of exercise in animal obesity[94] and in weight control in human subjects.[95] The importance of decreased physical activity in the development of obesity is, in particular, clearly shown in the obese-hyperglycemic mice,[94] in which it represents, from a thermodynamic standpoint, a more important factor than the slight degree of overeating that takes place. In obese children, similarly, intakes are not larger on a statistical basis than those in nonobese children, but physical activity appears to be considerably diminished.[96]

It is likely that indiscriminate assembling of many different forms of obesity of various etiologies under one heading has been responsible for the lack of progress in identifying specific metabolic abnormalities of etiologic significance in human obesity. Even the descriptive aspect of obesity has been neglected. Virtually nothing is known about age at onset or the course of the condition when it appears at different ages. Even knowledge about the different patterns of fat distribution in obese persons has been limited. In this regard, however, an effort at systematizing the available observations has been made by European authors. A commonly accepted classification[97] distinguishes an "android" type of obesity in which the excess fat is concentrated in the upper half of the trunk and secondarily in the abdomen and the mesentery. Such persons are frequently plethoric and display decreased activity and a large consumption of food. Hypertension, decreased glucose tolerance, hypercholesterolemia, hyperuricemia and renal disease are frequent complications in this group. By contrast, a "gynoid" type of obesity is described in which the excess fat is predominantly at the level of the hips and thighs. Other varieties are discussed. Regardless of the merits of this particular classification, the nosologic approach does help to stimulate analytic observation of obese patients, an essential step to better understanding of the whole problem.

An example of the importance of differentiation of obese patients of various types if significant metabolic abnormalities are to be discerned is provided by the findings of a recent study.[98] Two groups of obese women, believed to be representative respectively of "active" and "static" obesity, were compared with a similar group of subjects of normal weight whose height, age and socioeconomic environment were similar. The obese subjects were regarded as being in the "active" phase if they had been gaining appreciable amounts of weight at the time the study was performed, regardless of duration of obesity, or if their obesity was of relatively recent onset. "Static" obesity was defined as obesity of long duration (usually since childhood) and arrested for a long time, either spontaneously or by diet. It was found that, compared to the controls, the obese subjects in the "active" phase of obesity displayed a marked "increased tolerance" to carbohydrate after ingestion of self-selected meals and also after test doses of glucose. The highly significant differences found between the "actively" obese group and the controls strikingly decreased, however, if all the obese women, whether active or static, were included in the comparison.

Summary and Conclusions

An attempt has been made to select from the vast contemporary literature on nutrition topics relevant to clinical medicine. For the physician, the problem of ensuring that appropriate nutrients are delivered to the patient in effective quantities frequently outweighs all other considerations. Thus, the central issue in supportive nutrition, protein utilization, has been given major emphasis. From a consideration of the various factors that influence protein utilization it is possible to select useful principles that may be applied in the nutritional management of patients.

More frequently, the physician is confronted with the opposite disorder of overnutrition. The frustrating problem of obesity has too often been dismissed as a simple problem of "overeating," presumably to be cured by discipline. It is believed that obesity can best be placed in proper perspective by being viewed as an end product for which a number of different disturbances affecting energy balance can be responsible. In this regard, a better understanding of the normal physiologic mechanism that regulates food intake appears to be indispensable to a rational approach to the problem.

It has been pointed out that certain recent findings of nutritional research concerning protein, fat and carbohydrate metabolism are being applied with profitable results by physicians in the management of such disorders as uremia, celiac disease and diabetes mellitus.

Finally, it seems appropriate to predict that the role of nutrition in clinical medicine will continue to grow in importance as it becomes increasingly evident that many unsolved problems of management, treatment and prevention of disease can best be dealt with by utilization of the concepts and technics of the science of nutrition.

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MEDICAL INTELLIGENCE

WORKDAY OF THE SOVIET PHYSICIAN

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THE lot of the Soviet physician is not a happy one as judged from a long and detailed study recently published in the Soviet Union by the *Literary Gazette*, the influential and official organ of the Union of Soviet Writers. Entitled "Hours and Minutes of the Physician," the article reveals several grave shortcomings in medical work.

In the first place the patient load is so great that not even the *official* norm of 10 minutes for each can be observed by the physician. Thus, in 2 cases reported as typical, a physician saw 22 patients in 3 hours, and another saw 26 in 3½ hours. Needless to say, careful examination and even civil conversation with the patient are almost impossible. This time is further whittled down by the tremendous amount of paper work that must be done in the form of endless forms and statistics. Thus, of the 180 minutes spent by the first physician, 33 were devoted to listening to and examining patients (an average of one and a half minutes per person), 9 in measuring blood pressure, 56 in reading and filling in case histories and the rest, or about half, on paper work.

In a typical polyclinic, every month doctors must supply statistical figures, and every six months the polyclinic turns in a table that is 4½ feet long and contains 87 charts and 700 figures. No one, however, has been able to provide a satisfactory explanation of the use of these statistics by the Ministry of Health.

Furthermore, as a result of an order issued in 1949, physicians must work in inpatient and outpatient departments; this has meant an increase in the number of hours spent at work, and the typical day of the Soviet doctor is from 8 a.m. to 6 p.m. This has also led to a daily run from polyclinic to hospital and vice versa, with every physician overworked and watching the clock. In addition, almost every evening the physician must attend lectures or meetings for 2 more hours. Returning home at 8 p.m., he must complete the paper work not finished at the office. This takes an additional 2 hours. Since the majority of doctors are women, there is little time left for housework or for care of children.

Nor do doctors have enough time to carry on research work based on their daily routine, or to keep up with the medical journals. Physicians are also "borrowed" by the local organs of health for various assignments, thereby increasing the load on the other physicians, and many an experienced practitioner is put permanently behind a desk, where he has no chance to perform the work for which he was trained. Furthermore, the medical districts, which were originally designed to service 4000 people, now have 5000, 6000 and even 7000 people registered so that the lines in front of the doctors' offices are growing longer and longer whereas the number of doctors assigned to these districts has remained approximately the same. Medical propaganda has convinced the population to go and see

the physician "at the smallest discomfort." This further increases his load. It is thus doubly impossible for the physicians to enact prophylactic measures and to keep the entire population under observation as they are urged to. The authors of the article propose several measures to remedy the situation.

A month later, the *Literary Gazette* published a résumé of letters that had been sent in by readers in response to the article. Most of the letters confirmed the impression that the situation described was not a unique phenomenon, but typical of the entire Soviet medical setup. Letters particularly criticized the "paper flood" to which the doctor was subjected, emphasized the necessity of a careful examination and the value of conversation between patient and doctor, stating that "a psychotherapeutic talk sometimes has more effect than a spoonful of medicine," and urged a revision of the official 10-minute norm. Suggestions were also offered to keep physicians working for long periods in either inpatient or outpatient departments. Finally, the question of material rewards was broached. Doctors should receive more pay, their vacation time should be extended from 12 to 24 days a year, the Government should be more careful in seeing that the physicians get social recognition in terms of medals and orders, and finally the work and the life of the doctor should be improved to provide, in turn, for better care and health of the Soviet population.

The frankness of this criticism, unusual for a Soviet publication, may well indicate that the problem of the position and the work of the Soviet physician will receive more attention from the Government. Whether this will result in any appreciable improvement of his lot is still to be seen.

DOCTORS AFIELD

Alexander Anderson

ANDERSON NETTLESHIP, M.D.*

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THE title *Diarium Commentarium Vitae Alex. Anderson, Ann. 1793* is the beginning of a daily record that was to extend into the summer of 1799. Thus it was that Alexander Anderson, M.D., 1775-1870, labeled the first page of his diary, an account that was to reflect the formative years of this physician and engraver. It is a shame that an observer so accurate and objective did not record the last seventy-one years of his life. This man, known as the "Father of American Wood Engraving," had a keen view of life, which he imparted well in his writings. If he had put down the events through which he lived in New York from 1793 until 1870 American history would have been immeasurably benefited. But, for what it is worth, his five and a half years of diary stand as a clear picture of the people and his time. It also tells of the young man's feelings during seasons of happiness and despair: the happiness of a man of quiet habits, of family groups, of singing and playing the violin; and despair brought on by the yellow-fever epidemic of 1798, during which, in the space of a single month, all the members of his immediate family — brother, father, wife, mother and sister — died. Alexander Anderson survived all this sorrow and had years of prodigious creative work.

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The diaries were written in the port of New York during the period after the Revolution. Here crowded ships brought immigrants and supplies, as well as disease, to America. In this small, primitive colony building went apace. The alarms of fire were constantly heard. Fragments of old-world culture were to be found, and already a vigorous growth of new-world culture was taking place. Religion was here, old and new, and plays. There was the tragedy, accompanied always by the inevitable farce, and lectures of all sorts. Music was to be heard, even though much of it was martial — provided by the drum and fife corps. There was the Fly Market, a sort of animal circus or moving zoo and circus, as well as exhibits of large paintings and etchings. There was the public library and books, many books of all kinds. And there was the need for an engraver to enlarge the field of American book illustration. It was into this need, although he had been trained as a physician and had practiced medicine, that Anderson stepped with alacrity.

There are, of course, many ways of writing a diary. Alexander Anderson chose the route of fidelity of factual reporting. Through this technic of objective recording of facts all his emotions, feelings, desires and joys are clearly transmitted. Written when he was a physician's apprentice, medical student, intern and young practitioner, the diaries clearly show that he was from the beginning an artist as well. The very first sentence of the first diary reads, "Rose at 5 o'clock sat down by the fire with a tub of water and began to scower the copper plate . . . prepared it for engraving by breakfast time and worked at it till 10 o'clock." This sets the major theme for the whole of the diaries, for although medicine, sickness, disaster, fire and epidemics raged about him he was never far from his engraving tools.

The diaries furnish a picture of family life and family gatherings, eating and singing and talk, of a quiet father and brother and a neurotic mother, whom Anderson used for a model on which to base his doctor's dissertation. The shy courtship and marriage are also well pictured. One sees Anderson, too, as he served as a doctor's assistant, building the doctor's fire and delivering medicines. He helped his preceptor in medical rounds, supporting the

stump of a boy's leg that had been mangled by a bear (the leg was amputated below the knee). He saw lithotomies performed and marveled at the birth of triplets. There was much more. His description of medical students, their antics and the medical school is all so familiar it could have been written today. The medical-school courses and reading were advanced for the times and sound much like those of today, except they were much broader — the student then studied not only medicine, surgery and chemistry but also Latin, French, grammar and the classics. Finally, the long trial and preparation for

Courtesy of The Metropolitan Museum of Art

Alexander Anderson

graduation began. Public examinations were given and passed successfully, and then the dissertation prepared and accepted. At last a "license" to practice medicine was received.

Anderson's internship was at Bellevue (hardly the Bellevue of today!). At one time he saw the hospital converted into a house of "entertainment." At the time of his hospital stay New York was struck with repeated epidemics; he was tremendously depressed by the lack of efficiency of the medicines he used in these. His report of hospital admissions and deaths from yellow fever gives an accurate epidemiologic picture of the disease. He was never satisfied with practice and did a few autopsies, under much duress, on patients who had died of yellow fever. After his hospital stay he practiced medicine and here he gives a well rounded story of what that was like at the end of the eighteenth century. For example, he did trephining and got smallpox matter and inoculated children. He did obstetrics but had little taste for deliveries. He took care of the fatally ill. Skill with venereal diseases made him the sailor's friend.

He liked to take long walks, play the violin and go sailing on occasion. Through all this he never stopped etching and engraving; there is hardly a day's record that does not contain the entry of some engraving begun or finished. No subject that came to hand was too simple — tobacco stamps were done by the hundreds — and none were too complex.

Anderson was a restless sleeper and often got into trouble with violent night walking or drawer opening. But he always arose before daylight and engraved. He liked to work directly on metal objects such as compass plates or silverware. He illustrated and printed some small books, but these proved of no profit. He worked long hours over an anatomic figure 4 feet high.

His wife had a "stout boy," who lived for three months and succumbed to what would now be called summer diarrhea. A few weeks afterward, in late summer, the whole family except Anderson died from yellow fever. Even this did not stop Anderson from observing how the mortality of the disease increased within a few days during the epidemic. He consoled himself with a few tunes on the violin, drank a glass of wine and lay down to sleep. After arranging matters he took a trip to Stamford and returned. With relief he noted on November 1, "The snow has fallen." He traveled then to Bethlehem, Pennsylvania. He had a toothache. Later in the month he called on two young ladies. He engraved his mother's likeness from sketches and memory. He had a go at stone carving but worked more at engraving. In early February he sailed to Kingston for a visit with his uncle and family, but, being a typical New Yorker, he finally resolved on going home. He landed in Boston and took the stage for New York. On June 29 he reached the Harlem bridge and concluded his diary with this statement "... a pleasant ride brought me to my old quarters where I was kindly received, and enjoyed all the pleasure which the presence of old acquaintances and well known objects could afford...."

Thus, with dramatic abruptness, ends his diary, which perhaps because it so fully rounded out a cycle in Anderson's life could be carried no farther. It stands as its own statement of the development, tragic climax and final readjustment of this man's life to a harsh environment.

I am indebted to the Columbia University Library for permission to read the diaries, the original copies of which are part of its rare-book collection.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40051

PRESENTATION OF CASE

First admission. A sixty-year-old retired Greek bakery worker was admitted to the hospital for repair of an inguinal hernia. He had recently felt a sudden pulling sensation in the left lower quadrant after lifting a sack of flour and noted a swelling in the inguinal region.

The past history included an operation for "locked knee" three years previously at another hospital. The patient thought there had been "a lot of blood at the time." He had been treated for syphilis after positive blood Hinton and Wassermann tests at another hospital thirteen years before admission; numerous spinal-fluid examinations were negative. The serologic tests never reverted to negative, however. When he was studied for epigastric pains a year before admission, he was told he had a gastric ulcer and was treated with a diet, which he did not follow. The symptoms left, however. He had always worked in bakeries or as a laborer.

Physical examination showed a well developed and well nourished man. There were a few slightly enlarged anterior cervical lymph nodes; the chest was clear. The heart was not enlarged; there was a Grade 1, soft, apical systolic murmur. The liver edge was not palpable, but the spleen was felt 1 fingerbreadth below the left costal margin. There was a bulge in the left inguinal region that was reducible.

The temperature was 98.6°F., the pulse 70, and the respirations 18. The blood pressure was 140 systolic, 80 diastolic.

Urinalysis was normal. Routine blood studies demonstrated a hemoglobin of 16.0 gm. per 100 cc. and a white-cell count of 14,600, with 72 per cent neutrophils, 11 per cent small and 5 per cent large lymphocytes, 3 per cent monocytes, 8 per cent eosinophils and 1 per cent basophils. There were occasional polychromatophils, and the platelets were increased. The serum protein was 6.2 gm., and the nonprotein nitrogen 32 mg. per 100 cc. The prothrombin time was 23 seconds (normal, 15 seconds), and the clotting time and clot retraction were normal. The blood Hinton test was positive. A stool was guaiac negative.

The night after herniorrhaphy, a large hematoma developd in the wound; this had to be evacuated surgically. A single 500-cc. transfusion returned the hemoglobin to its preoperative levels, and he was discharged two weeks later.

Second admission (three years later). The patient was admitted to the hospital with the complaint of a sour stomach for many months and because during his outpatient visit splenomegaly was again found.

He had noted a gradual decrease in appetite over the past three years, with weight loss, fatigue and occasional soaking sweats. In addition a steady, sharp, boring pain under the right costal margin anteriorly had developed about three months before admission. Also, the abdomen had gradually increased in size. He relieved this pain, which occurred an hour to an hour and a half after meals, by lying down or by taking soda and omitting the next meal.

On physical examination the liver was palpable 2 fingerbreadths below the right costal margin, and the spleen filled the left side of the abdomen. It had an easily palpable notch and was firm, smooth and moderately tender.

Urinalysis was negative. The urinary urobilinogen was 0.3 Ehrlich units per two-hour specimen. Examination of the blood revealed a hemoglobin of 11.0 gm. per 100 cc. and a white-cell count of 13,000, with 39 per cent adult neutrophils, 15 per cent band forms, 7 per cent small and 10 per cent large lymphocytes, 4 per cent monocytes, 5 per cent eosinophils, 5 per cent basophils, 10 per cent myelocytes and 5 per cent normoblasts. There were 10 per cent reticulocytes and hypochromia, anisocytosis and poikilocytosis of the red cells with normal platelets. The total protein was 6.5 gm. (albumin 4.2 gm.), the nonprotein nitrogen 25 mg., the bilirubin 0.8 mg., the calcium 9.4 mg., the phosphorus 5.4 mg., the alkaline phosphatase 2.4 Bodansky units and the uric acid 5.7 mg. per 100 cc. Cephalin flocculation was +++ in forty-eight hours. A stool was guaiac negative. A quantitative blood Hinton test was positive in a titer of 1:64. An electrocardiogram was within normal limits. Roentgenograms of the chest demonstrated clear lung fields and a normal-sized heart. The bones of the thorax, particularly the ribs, were denser than normal. A gastrointestinal series was normal except for displacement of the stomach by the enlarged spleen.

An iliac-crest bone-marrow aspiration was unsuccessful, but aspiration of a spinous process yielded bone marrow that showed abundant megakaryocytes, 65 per cent myeloid cells, with a shift to the right, 29 per cent erythroid cells and 6 per cent

lymphocytes. No tumor cells were seen. The patient was discharged after a ten-day stay.

Third admission (seven months later). He entered the hospital complaining of progressive abdominal swelling over the past four months, along with continued anorexia and distention after eating. He also had urinary frequency.

Physical examination was unchanged except for wasted facies, ascites, orthopnea and dullness and decreased breath sounds at the right base. There was ++++ edema of the legs extending to the sacrum.

The routine laboratory studies were unchanged. The bromsulfalein test showed 5 per cent retention; the urinary urobilinogen was 3.0 units per 100 cc. and a Coombs test was negative. Other tests were as before. Paracentesis yielded 6000 cc. of opalescent, yellow fluid containing 150 mononuclear cells per cubic millimeter. The symptoms were much relieved. Repeated questioning failed to reveal a history of exposure to bone-marrow toxins. Biopsy of a left axillary lymph node was reported as showing chronic lymphadenitis and reticular hyperplasia. A splenic aspiration disclosed a profusion of red-cell precursors. A barium-swallow examination demonstrated large esophageal varices. The patient was discharged to be followed in the Out Patient Department.

Final admission (eight months later). In the intervening period he had twenty-three abdominal paracenteses at almost weekly intervals, with the removal of about 5000 cc. of clear fluid each time. Despite salt restriction, diuretics and paracenteses, fluid continued to reaccumulate, and he became weaker. About a month before admission diarrhea developed, becoming severe four days before admission. He had had noncrampy, diffuse abdominal pains and ten to twelve stools a day.

With the exception of increased emaciation, the physical findings were the same as on the previous admission.

The temperature was 98.6°F., the pulse 110, and the blood pressure 85 systolic, 60 diastolic.

Routine blood studies showed a white-cell count of 27,000, with 31 per cent neutrophils, 40 per cent band forms, 6 per cent myelocytes, 6 per cent blasts and 6 per cent basophils.

Culture of ascitic fluid grew out *Staphylococcus aureus,* and penicillin therapy was begun, along with streptomycin and subsequently chloramphenicol. Penicillin was given intra-abdominally. The patient gradually became weaker and less responsive over the next month, with decreasing oral intake. He was maintained with parenteral administration of fluids and antibiotics. Repeated cultures of ascitic fluid grew out *Staph. aureus* and nonhemolytic streptococci. He died quietly on the forty-fifth hospital day.

Differential Diagnosis

Dr. William H. Baker*: This sixty-one-year-old man had a progressive disease involving the spleen and liver with the appearance of immature cells of both the red-cell and white-cell series in the peripheral blood and the terminal development of recurrent and relentless ascites. This process can be divided into two phases: the first occurred over a period of three years, during which the disease progressed slowly, and the second over a period of fifteen months, during which the symptoms progressed more rapidly to death.

A year before the first admission he was said to have had a gastric ulcer, which perhaps is a "red herring" because there was no evidence throughout the remainder of the history that a gastric ulcer existed. The fact that he worked in a bakery probably had little to do with the subsequent illness. The important finding was that the spleen was felt 1 fingerbreadth below the costal margin and progressively increased in size over the next four and a half years. At this time the hemoglobin was 16 gm. per 100 cc., and over the succeeding three years it dropped to a low level. Also, he had an elevated white-cell count, which is consistent with inflammatory changes within the inguinal hernia, but in view of the subsequent course I think the increased white-cell count is significant. Another pertinent point is that, in spite of the platelet increase, the prothrombin time was reported as 23 seconds with a normal of 15 seconds. It is unusual that the prothrombin time was not repeated and that vitamin K was not given before the operation. I do not know how to interpret the prolonged prothrombin time at this stage of the disease. It was suggested throughout the history that there was a bleeding tendency, and that impression is substantiated by the fact that a large hematoma developed after the operation.

In the three-year interval this patient, although he was relatively well, intermittently had weight loss, fatigue and occasional soaking sweats. These constitutional symptoms, of course, are those of any diffuse pathologic process. Tuberculosis certainly could have caused these symptoms. Miliary tuberculosis in the adult is rarely diagnosed ante mortem. Malignant lymphoma, especially Hodgkin's disease, could have produced these symptoms, as could carcinomatosis. The steady, boring pain in the right costal margin that occurred intermittently through the remainder of the course is suggestive of a carcinoma of the pancreas. The fact that the pain was relieved by lying down is somewhat against a pancreatic neoplasm. Although the pain with a pancreatic neoplasm can be of any character, it usually radiates to the back and is relieved when the patient stands up or bends over.

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At the time of the second admission, the liver had become palpable and the spleen filled the entire abdomen. This is quite an increase in size over three years. The patient had an anemia that was not severe. The white-cell count again was slightly elevated, and there were immature white cells and normoblasts in the peripheral blood. This is most significant, suggesting some type of disorder in the myeloid series of cells. At this time there was reticulocytosis, suggesting an increased red-cell destruction. The Coombs test at a later date was negative; it was not done at that time, but the urinary urobilinogen was normal. A determination of urinary urobilinogen is not a valuable test of hemolytic anemia because it is nonspecific, has to be done on a fresh specimen and is subject to a great deal of error. Moreover, it can be elevated with constipation and various other disorders that physicians are not especially looking for when they request the determination. The test is helpful but not diagnostic of any disease. I do not mean to skip over the phosphorus of 5.4 mg. per 100 cc.; that was definitely elevated and may have been related to the underlying disease. Since this determination was not repeated and confirmed it is difficult to interpret. The uric acid of 5.7 mg. per 100 cc. is at the upper limit of normal and probably consistent with the process that this man had; uric acid elevations are found in destructive lesions of the red or white cells, leukemia, polycythemia vera, myeloid metaplasia and gout. The serologic tests were positive, and treatment was given. I am interpreting this to mean that the patient was treated for syphilis with successful suppression of activity but no reversal of the positive serologic tests.

The bones of the thorax, especially the ribs, were denser than normal. May we see the x-ray films now?

Dr. Stanley M. Wyman: The first examination of the chest shows clear lungs and a heart of normal size and shape. The ribs, however, look denser than usual; they have a uniform chalky appearance. I do not see any areas of destruction or any areas of localized increased density. Examination of the gastrointestinal tract done on the second admission shows the tremendously enlarged spleen overlying the iliac crest and displacing the stomach to the right of the midline, the duodenal cap and loop lying quite far to the right. The liver is not seen on these films. Varices are suggested at that time and are definitely present on the examination done seven months later. At the time of the second admission the chest is smaller because the ascitic fluid in the abdomen is pushing the diaphragm up. Again, the bones are definitely whiter and therefore denser than normal.

Dr. Baker: Do you think you would notice that increased density if you were looking at a routine chest film? This chest film itself seems to be a little denser.

Dr. Wyman: That is a difficult question to answer now when we know the whole clinical picture; however, I think that these bones are denser than normal. This is borne out by the last film, in which the ribs are seen through the very large spleen. The increased density of the spine and pelvis is a little less striking. I do not see any evidence of a gastric or duodenal ulcer; the duodenal loop seems normal in size and shape. If there is disease in the pancreas, I do not recognize it. On the pyelogram, which is not recorded in the protocol, the right kidney is slightly smaller than usual. The calyceal system does not show any localized abnormality. The abdominal aorta is sclerotic, which is not unusual in a man of this age. There is surprisingly little degenerative change in the spine for a laborer. This later chest film again demonstrates the diffusely dense ribs.

Dr. Joseph C. Aub: The spine does not show the increased density.

Dr. Wyman: It is difficult to be sure of that. We are seeing the spine through a large, ascitic abdomen, and those bones are quite well visualized for such an examination. The ribs are denser than one expects and remind me of the picture we have seen with sickle-cell anemia with tiny bony infarcts, fluorine poisoning or myeloid metaplasia.

Dr. Baker: I shall accept the fact that there was increased density of the bones.

The iliac-crest bone-marrow aspiration was unsuccessful but aspiration of the spinous process revealed abundant megakaryocytes in the bone marrow and 65 per cent myeloid cells with a shift to the right, which means an increase in maturity of the myeloid cells. The 29 per cent erythroid cells is within approximately normal limits. One has to define the type of myeloid cells seen and the percentages before one can say that 65 per cent is absolutely normal, but certainly at this point no diagnosis of myelogenous leukemia or any other process could be made. The fact that no tumor cells were found is somewhat gratifying, but tumor cells may be present throughout the bone marrow and not be found at one aspiration.

During the final admission, the pertinent points are the extensive peripheral edema and ascites, the normal bromsulfalein test, which I consider the best single test of liver function, and the slightly elevated urine urobilinogen, which is consistent with an accelerated destruction of red cells. Paracentesis yielded 6000 cc. of opalescent fluid containing 150 mononuclear leukocytes per cubic millimeter. I assume that no tumor cells were found. I should like to know the specific gravity and the total protein of the fluid — especially the total protein in view of the fact that about 115,000 cc. of fluid was removed over the thirty-two weeks. If the total protein was high it

means considerable loss of protein from the paracenteses.

DR. BENJAMIN CASTLEMAN: The protein of the ascitic fluid was 2.5 gm. per 100 cc., but infection was present at that time.

DR. BAKER: That is a high level. I suspect that the serum protein fell during the last admission.

An important negative finding was a biopsy of a lymph node, which showed only chronic inflammation and slight reticular hyperplasia. Of course lymphoma could have been present elsewhere. The splenic aspiration demonstrated a profusion of red-cell precursors. I assume that 100 per cent of the cells were erythrocyte precursors. This is significant and pertinent to this man's disease. The development of ascitic fluid, without the presence of a lowered protein or any indication of cirrhosis, and the presence of the esophageal varices suggest portal hypertension that was not of hepatic origin or due to altered serum protein but was caused either by the partial thrombosis of the portal vein or by pressure on the portal vein. I attribute the severe diarrhea to the same etiologic process — namely, venous thrombosis in the mesenteric vessels. Finally a *Staph. aureus* infection of the ascitic fluid developed, which I suppose Dr. Edward H. Cass, of the Boston City Hospital, would call iatrogenic. Unfortunately, as so often occurs the organism was undoubtedly resistant to penicillin.

To put this entire progression of symptoms together, I believe that the enlargement of the spleen, which was enormous in the final stage of the disease, the gradual enlargement of the liver, the presence of immature cells in the peripheral blood and the normal bone marrow with a predominance of the myeloid series mean that this man had myeloid metaplasia. This condition has twenty synonyms or more and is at present regarded not as a disease entity but as a stage in a group of conditions called the myeloproliferative disorders. Many people believe that polycythemia vera, myeloid metaplasia, myeloid leukemia and other, more obscure myeloproliferative disorders are probably a single entity with a progression in some cases from one to the other. They certainly resemble each other in many respects, and I believe that they are probably close relations of a basic disorder. I interpret the ascites and the eventual diarrhea as due to partial portal-vein thrombosis, mesenteric-vein thrombosis and staphylococcal peritonitis. I cannot rule out pancreatic carcinoma as the "sleeper" in this clinicopathological conference, but I am not going to make that diagnosis.

DR. JACOB LERMAN: I might add that terminally the patient began to bleed from the gastrointestinal tract.

DR. BERNARD M. JACOBSON: As I recall, a very obscure fever that is not mentioned in the protocol was present through most of the hospital stay. The physicians on the service were worried about lymphoma; that was the reason for the biopsy.

DR. BAKER: Lymphoma is a better possibility in view of the fever; I did not know about that. I shall still choose myeloid metaplasia with partial portal-vein thrombosis and mesenteric-vein thrombosis.

CLINICAL DIAGNOSES

Agnogenic myeloid metaplasia.
Peritonitis, subacute.
Toxic encephalopathy.

DR. WILLIAM H. BAKER'S DIAGNOSES

Myeloid metaplasia.
Portal-vein thrombosis, partial.
Mesenteric-vein thrombosis.
Staphylococcal peritonitis.

ANATOMICAL DIAGNOSES

Agnogenic myeloid metaplasia, with extramedullary hematopoiesis in spleen, liver, kidney and para-aortic lymph nodes, and diffuse myelofibrosis and myelosclerosis.
Splenomegaly.
Portal hypertension, etiology undetermined, with esophageal varices and ascites.
Peritonitis, acute and chronic.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy confirmed the diagnosis that was made both on the ward and by Dr. Baker

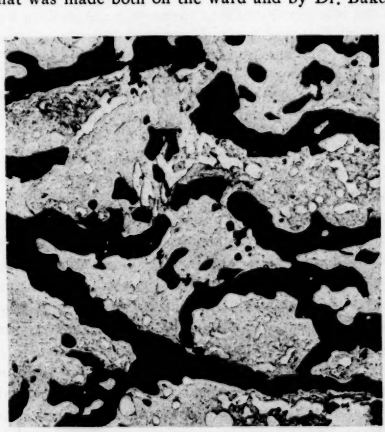

FIGURE 1.

— that is, a condition that we call myeloid metaplasia for want of a better term. The bones were all very sclerotic. A section from a vertebra showed the fat and marrow elements replaced by loose connective tissue and fibrin — what Dr. Baker called the mye-

loproliferative phase — and a marked increase not only in size of the bone trabeculae but also in their number, without any evidence of activity of the osteoblasts (Fig. 1 and 2). Since there was no lining up of osteoblasts such as one expects in the conditions that are actively forming bone this must have been a slow process of bone formation, stimulated

FIGURE 2.

apparently by the myeloproliferative reaction in the marrow.

A PHYSICIAN: Were there any osteoclasts?

DR. CASTLEMAN: Very few osteoclasts or Howship's lacunae. The bone looked inactive and perfectly normal except that there was more of it. There was little marrow left and certainly a marked atrophy of the marrow elements.

The liver weighed about 1850 gm., — only slightly above normal, — and the spleen 1600 gm., — tremendously enlarged. Microscopical examination revealed throughout the spleen extensive hematopoiesis, primarily of the red cells although there were some myeloid elements. There was no cirrhosis of the liver. There was some hematopoiesis in the liver and some fibrosis around a few of these cells but apparently not enough to cause the portal hypertension, which I cannot explain. We found no thrombosis in any of the splenic or mesenteric veins. The ascitic fluid was voluminous and infected and was certainly a major cause of death.

DR. BAKER: Do you think that there was pressure on the veins to account for the signs of portal hypertension?

DR. CASTLEMAN: That may have been one factor. We were unable to determine the etiology of the myeloid metaplasia. There was no evidence of exposure to benzene; patients whom we have seen with this intoxication show exactly the same picture — a myelofibrosis. We had always been under the impression that the hematopoietic changes in the spleen and liver were secondary and compensatory to the destruction of the bone marrow; more recently, some authorities have stated that whatever is irritating, stimulating or destroying the bone-marrow elements is doing the same thing to the reticuloendothelial elements in the spleen, liver and lymph nodes so that the reaction is a diffuse one throughout the body and not necessarily hematopoiesis secondary to bone-marrow destruction.

DR. WYMAN: Regarding the question of whether or not the bones were originally interpreted as being denser than normal, our official interpretation was as follows: "The findings are those of tremendous splenomegaly and a definite suggestion that the bones are somewhat denser than usual. The appearance suggests myeloid metaplasia."

CASE 40052

PRESENTATION OF CASE

First admission. A seven-year-old boy was admitted to the hospital because of pain and swelling in the axilla of three days' duration.

He had apparently been well until four days before admission, when he was struck in the right axilla by a football. On the following day, he noted some swelling with pain and tenderness in the right axilla.

Physical examination revealed a well developed and well nourished boy. There was a 5-mm., firm, nontender papule with a hard, gray, discrete, depressed 1-mm. center on the dorsal aspect of the first interosseous web of the right hand. Surrounding the papule was a small zone of erythema. The forearm was not tender or red, and the epitrochlear lymph nodes were not palpable. There were at least three palpable lymph nodes in the right axilla, the largest of which measured at least 5 cm. in diameter, that were tender but not fluctuant. There was also slight adenopathy in the left axilla, but cervical and inguinal adenopathy was minimal. The remainder of the examination was negative.

The temperature was 99.8°F., the pulse 96, and the respirations 24. The blood pressure was 100 systolic, 60 diastolic.

Urinalysis was normal. Routine blood studies showed a hemoglobin of 13 gm. per 100 cc. and a white-cell count of 8200, with 64 per cent neutrophils, 27 per cent lymphocytes, 8 per cent monocytes and 1 per cent eosinophils. The sedimentation rate was 31 mm. in one hour. The old-tuberculin skin test in a dilution of 1:1000, the Frei test and

heterophil-antibody agglutination were negative. A culture of the papule showed no growth.

Direct questioning of the patient about the origin of the papule was unrewarding. He said that he had noted it ten days before admission but paid no attention to it; however, he did not remember any insect bites, injury or other possible cause. On the second hospital day, the temperature rose to 101.2°F., with no constitutional symptoms. Thereafter, the temperature curve was irregular, with elevations to 100°F. despite the administration of 600,000 units of penicillin daily for six days. Two additional white-cell counts were in the range of 11,500, with 75 per cent neutrophils. The papule in the hand and the enlarged axillary lymph node remained unchanged. At that time the patient was discharged to be followed at the clinic.

Final admission (three weeks later). At the time of a clinic visit two weeks after discharge the temperature was 100°F. The axillary lymph node was approximately the same size as before and was nontender. On the day of admission the mass in the axilla was noted to be larger, with increased tenderness and redness. In addition there had been a 2-pound weight loss; however, fever, anorexia and malaise were denied.

Positive physical findings were limited to the right axilla, where there was a 6-cm. firm, tender mass over which the skin was red but freely movable.

The temperature was 99.2°F., and the pulse and respirations normal.

Urinalysis was negative. The hemoglobin was 12 gm. per 100 cc., and the white-cell count 12,800, with 62 per cent neutrophils.

On the second hospital day an operation was performed.

Differential Diagnosis

Dr. George L. Nardi*: This is a straightforward story of two lesions, one on the dorsum of the hand and the other of the axillary lymph nodes. I think the crux of the problem is whether or not the two lesions were related. Both these lesions can be classified as tumors, and generally any tumor falls into one of four groups: congenital, inflammatory, neoplastic or traumatic. Certainly, this was not a congenital lesion.

First I shall discuss the bizarre papule on the dorsum of the hand. Merely because the child denied trauma is no reason to believe that the lesion was not traumatic. The description fits a so-called inclusion cyst, a foreign-body reaction from local low-grade infection. Among the inflammatory lesions tuberculosis comes to mind. So-called anatomic tubercles on the hand do occur, but apparently there was some rubor and calor and this does not fit with tuberculous infection. There is a whole list of acute inflammatory processes that produce benign lesions of the hand, none of which, I think are applicable here. I do not believe it was tularemia. Various mycotic infections may give this sort of picture. I might consider a so-called pyogenic granuloma, which is not at all as described here, but is a rather friable, bloody, strawberry-colored tumor. I shall discard these unusual inflammatory lesions.

Among the neoplastic lesions are the xanthomas and fibromas. Benign tumors of the hands are relatively rare, and the malignant ones are even more uncommon in this age group. I shall say no more about them, because I do not think this patient had a neoplastic lesion.

Were the enlarged lymph nodes in the axilla inflammatory and secondary to the lesion in the hand, or were they unrelated? Was this change in the axillary lymph nodes neoplastic? There were minimally enlarged lymph nodes elsewhere. One thinks of the entire group of lymphoma — leukemia, Hodgkin's disease and so on. The blood picture, from what little I know about those diseases, does not seem to fit with that. The spleen and the liver were apparently not palpable. The patient had no anemia and seemed to be in excellent health. He was playing football when he was struck in the axilla. I am inclined to believe that the lesions in the axilla were inflammatory, acute or chronic, and that the redness that developed was caused by periadenitis of the axillary lymph nodes. My inclination is to call the lesion on the hand an inflammatory lesion, perhaps either a foreign-body reaction or an inclusion cyst, with the development of chronic lymphadenitis in the axilla. I believe axillary lymph nodes were excised. Even though one considers a lesion inflammatory the only way to be sure that a potentially more dangerous lesion is not present is to excise it.

Dr. Allan M. Butler: Was there an x-ray film of the chest?

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DR. C. C. WANG: No x-ray films were taken.

DR. ROBERT S. PALMER: Where did he come from? Was he a country boy who was hunting and skinning rabbits or a Boston boy?

DR. JOSEPH R. PETRANEK: He was a Boston boy, but he had spent a summer on a farm, where he had had contact with various animals. The onset of the illness was noted at the beginning of the school year when he returned.

DR. PALMER: He may have been playing with sick rabbits.

DR. STEPHEN M. KRANE: Was he playing with cats? There is a cat scratch that produces a local adenopathy — the so-called cat-scratch fever.

DR. WINFIELD S. MORGAN: Apparently, the physicians tried to get that information, but I am not sure whether they were able to establish definitely that the patient had been in contact with cats.

DR. PETRANEK: There were cats at the farm.

CLINICAL DIAGNOSIS

Lymphadenopathy secondary to trauma.

DR. GEORGE L. NARDI'S DIAGNOSIS

Inflammatory lesion of hand, with secondary lymphadenitis.

ANATOMICAL DIAGNOSIS

Cat-scratch disease of hand and axillary lymph node.

PATHOLOGICAL DISCUSSION

DR. MORGAN: Dr. Kunz was most helpful in making the diagnosis in this case.

DR. LAWRENCE J. KUNZ: Dr. Petranek suggested the diagnosis; all I did was to write to Washington for some skin-test antigen for cat-scratch disease.* As everyone has probably guessed the skin test on this patient was positive.

DR. MORGAN: At operation the surgeon removed an axillary lymph node measuring about 1.5 cm. in diameter. Half of this was sent to the Department of Bacteriology for the preparation of additional antigen, and half to the Department of Pathology for histologic study. Microscopically, there was complete obliteration of the normal lymph-node architecture by a diffuse granulomatous process. The granulomas ranged from small to rather large ones, and varied in shape. These lesions were composed of eosinophil-staining, structureless material and cellular débris centrally, with a palisading of epithelioid cells at the periphery. No giant cells of the Langhans type were seen. The tissue between the granulomas was heavily infiltrated by mononuclear cells with fewer numbers of neutrophils, lymphocytes and eosinophils. Stains for tubercle bacilli were negative.

This is a nonspecific type of reaction, and I do not believe we have had sufficient histologic experience with the lymphadenitis found in cat-scratch disease to be able to say whether there are any particular features by which it might be differentiated from certain similar lesions, including tularemia or lymphogranuloma venereum.

DR. BUTLER: Would Dr. Kunz comment on the number of such cases we have had and the efficacy of skin tests in establishing the diagnosis?

DR. KUNZ: Since this case, which occurred in early October, the Children's Medical Service has turned up a total of 8 cases that, if they had not been recognized as cat-scratch disease, probably would have caused criticism of the Department of Bacteriology for not being able to isolate the staphylococcus or whatever organism was suspected by the clinicians. Each of these cases was diagnosed by means of skin-test antigen, and contrary diagnoses were excluded by other tests.

The disease is thought to be caused by a virus that is related to those producing lymphogranuloma venereum and psittacosis. As yet there have been no successful attempts to isolate such a virus. The Frei test is consistently negative in cases that are positive to the antigen of cat-scratch disease, but in some series the complement-fixation test for lymphogranuloma venereum is positive in varying percentages (in some series as high as 80 per cent and in others as low as 20 per cent). From 4 of our patients we prepared skin-test material, which Dr. Mary N. McGovern and the Children's Medical Service are preparing to test on patients along with the material sent to us from Washington so that we may carry the diagnostic chain on with our own antigen.

The question has been brought up regarding the specificity of the skin-test reaction. Pus from these patients is not usually obtained in large amounts, and for that reason it is usually tested in patients on whom the diagnosis is suspected; therefore, controls have been few. In any case in which controls have been tested at all, however, they have been con-

*The antigen was kindly supplied by Dr. Worth B. Daniels.

sistently negative. In one series 21 patients with disease other than cat-scratch fever, including illness in which the lymph nodes were involved in the same type of picture, have been tested and have been negative.

DR. MORGAN: This disease was apparently first recognized in France about 1930[1] and has since been observed in India as well as in many parts of this country. It is probable, therefore, that its distribution is worldwide. Daniels and MacMurray,[2] in 1952, reported 60 collected cases, the largest number studied in this country. In their series all but 5 of the patients had had contact with cats; 33 gave a history of having had a scratch in the region drained by the involved lymph nodes. In 35 of the patients the lymph-node involvement was axillary. Systemic manifestations were variable, but two thirds of the patients had complaints besides the adenopathy; most often these consisted of malaise, anorexia, nausea, weakness, lassitude, aching, chills or chilly sensations and headache. In 6 patients a rash developed. Two thirds had fever, which was usually mild, but in some cases the temperature exceeded 104°F. It was believed that absence of fever usually signified lack of sepsis in the lymph nodes. Since the incidence of fever seems to be variable in these cases cat-scratch disease is probably a more appropriate name than cat-scratch fever. In 41 of the cases reported by Daniels and MacMurray in which white-cell counts were done 32 fell in the range of 7500 to 13,000; only 5 were above 13,000. A final interesting observation in this study was that on examination all the cats from the affected households were well, and it therefore appears that the transmission of the disease is a passive one as far as the cat is concerned.

DR. BUTLER: What was the duration of the adenitis in this series?

DR. MORGAN: Quite variable. It may remain for several months.

DR. NARDI: Was the diagnosis known before the operation was done in the case under discussion?

DR. MORGAN: I think it was suspected, but the biopsy was done to help confirm the diagnosis.

DR. KUNZ: The antigen came about the time that the operation was performed.

DR. NARDI: I wonder whether the operation would have been performed if the diagnosis had been made?

DR. KUNZ: I think that the operation on the lymph nodes relieved the situation somewhat in a good number of cases reported in the literature.

DR. PALMER: Is there any antigenic or other than symptomatic treatment?

DR. MORGAN: No; not that we know of. This seems to be a self-limited condition.

DR. BUTLER: If I am not mistaken the policy of the Children's Medical Service and the Surgical Service is to drain these lymph nodes if the fluctuation is such that one is led to believe that there is considerable pus and otherwise to let them alone.

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PRESIDENT'S HEALTH MESSAGE

THE President's health message delivered to Congress on January 18 indicates a temperate consideration of the health needs of the nation and the part that the present administration believes the federal Government should play in meeting them. Mr. Eisenhower is firmly against "socialized medicine" — a loose term but one that is now generally interpreted to mean a Government-operated tax-supported plan for the prepayment of medical care for all who wish to avail themselves of it.

Legislation for which the President asks would include extension of social-security benefits to include physicians and dentists, liberalization of income-tax exemptions for medical expenses, increased Government leadership and participation in vocational rehabilitation, strengthening of Public Health Service research activities, more aid to the states to improve health and welfare services and medical facilities, and a "reinsurance" plan through which the Government will give added financial support to voluntary organizations for prepayment of medical service.

Although the organized medical profession has repeatedly expressed its opposition to its inclusion in old-age and survivors' insurance and will consequently be especially interested in this part of the message, the President's "reinsurance" proposal stands as the most important and possibly the most controversial recommendation. Under this plan the Government would set up a national health-insurance corporation to underwrite unusual risks and permit protection to be extended to very low income families. Such an idea is not emerging for the first time; four years ago Congressman Wolverton, now chairman of the House Interstate and Foreign Commerce Committee, submitted a bill containing similar provisions. Proposed during a period when the Government held more expansive views on such matters than at present, this bill was not acted on even by the committee.

The President's message asks for an increased participation of government in the provision of health and medical services to the people, with the purpose of improving such services without recourse to a general compulsory plan, which is still odious to a majority of the people. Individual approval or disapproval of this recommendation will be based on varied concepts of the proper function of government; whether as an agency that shall interfere to a minimum degree with the lives, activities and welfare of the country's citizens, or as one that shall assume the responsibility of attempting to ensure the greatest good to the greatest number.

More and more the demand is for increased participation; the popular concept of democratic government will not permit it to disregard the welfare of the governed. This is despite the dangers inherent in a paternalistic system that may weaken the fiber of a people and eventually sap its initiative. In the last analysis, regardless of factional disputes and group pressures, the people will get from their government much of what they demand.

Never has a consideration of the softening effects that such a course may have on future generations tempered those demands.

Always there exists a middle ground, such as Mr. Eisenhower is seeking, that may be effective from time to time; his type of leadership is of particular value, for its object is to direct popular demand into realistic and conservative channels. Out of the tangled web of the social and economic relations of medicine some constructive design may yet be emerging, favorable to the needs of its period.

CURRENT STATUS OF CHEMOTHERAPY OF TUBERCULOSIS

An experiment probably unique in clinical therapeutics, and certainly one of the most fruitful, is the study of the chemotherapy of tuberculosis conducted over a period of years by the Veterans Administration in co-operation with certain Army and Navy installations. This investigation has provided definitive answers to important practical questions concerning the application of potentially useful therapeutic agents. It has succeeded in joining in a common interest groups of workers in fifty widely separated hospitals, and fostering the spirit of objective inquiry without which it would not be possible to follow set protocols and without which, in turn, the results could hardly be meaningful.

The findings of this co-operative study were presented in detail at a series of conferences at which the results were critically analyzed and after which working protocols were revised and further studies instituted. As a consequence, the findings and deductions have furnished the most reliable and definitive answers to such questions as the proper dosage and duration of treatment with streptomycin, the efficacy of certain other chemotherapeutic agents and the optimum methods of using them, alone or in various combinations, in the treatment of pulmonary and other forms of tuberculosis. Many new questions have been tackled in the course of these studies, including the value of surgical procedures and the optimum methods of chemotherapy in conjunction with such procedures. Old and accepted procedures are being evaluated for their importance under current circumstances.

Two of the workers who have been most active in the development and prosecution of these studies recently presented carefully documented summaries concerning the chemotherapy of pulmonary tuberculosis. Tucker[1] described the results of the co-operative and controlled study designed to establish the relative value of different agents and dosage regimens and of the factors influencing these results. D'Esopo[2] likewise reviewed the position of the major chemotherapeutic agents now used in the treatment of tuberculosis as brought out in the Twelfth Conference, held in February, 1953. In particular, he discussed the relative merits of streptomycin, para-aminosalicylic acid and isoniazid, but he also briefly considered several lesser drugs such as viomycin, oxytetracycline and pyrazinamide. D'Esopo also stated some of the problems regarding the optimum duration of chemotherapy together with the protocol designed by the Twelfth Conference for the study of this point for which he was primarily responsible. His report reviewed the recent data concerning the viability of tubercle bacilli from closed necrotic lesions and discussed the significance of this problem in clinical practice. Moreover, the present status of the treatment of tuberculous meningitis and miliary and renal tuberculosis, on the basis of the data that were presented at that conference, as well as projected studies dealing with integration of pneumoperitoneum and chemotherapy and of bed rest and chemotherapy, was evaluated.

These two reviews should be carefully studied not only by physicians who are likely to undertake the treatment of tuberculosis but also by those who may be confronted with tuberculous patients and who require proper guidance to obtain the greatest advantage of recent developments in this field.

The conference to be held February 7-11 in St. Louis should be particularly interesting and stimulating. More detailed answers to pending questions concerning chemotherapy may be expected. The preliminary results of the attempts to control adjuvant therapy, such as rest and pneumoperitoneum, as discussed by D'Esopo,[2] will also be evaluated. These studies have required explorations into the methodology of clinical investigation, and some of them represent new ventures in the field of co-operative research.

REFERENCES

1. Tucker, W. B. Review of current status of chemotherapy of tuberculosis. *Ann. Int. Med.* 39:1045-1061, 1953.
2. D'Esopo, N. Chemotherapy of tuberculosis in man. *J. A. M. A.* 154:52-59, 1954.

RACE AGAINST TIME

As one walks the streets of nearly any well ordered American city with eyes occasionally cast down in a simple protective reaction, one is struck by a curious phenomenon. This is the presence, on street and sidewalk, of a generalized gray exanthem of nearly flat papules, each about an inch in diameter. It is as if a shower of putty had passed over the city precipitating drops of a uniform size, coming in little squalls, for the rash is so dense as to be nearly confluent in certain places — outside ball parks, at the entrances to subway stations, and moving-picture theaters, and around the doorways leading into stores and hotels.

This ineradicable pattern is not the result of a rain of putty, however, falling on the city like volcanic ash; it represents the end product of the now practically universal American habit of gum chewing. It is the *productus masticatus Americanus* of all time, and who can say that it serves no useful purpose?

For it gives to each citizen of the United States, like Father William, a muscular strength to his jaws that will last the rest of his life, without going to the trouble of arguing at the law. It adds, moreover, a regular increment to the fundamental physical stability of each municipality, which may in the long run serve it to good purpose.

For cities raise their ground levels at the rate of about a vertical foot a century — the floors of ancient Londinium are 20 feet below the street level of modern London — and a mixture of well masticated chewing gum will not only conceivably increase the rate of this growth, but will certainly bond the material into an indestructible matrix. It is a case of the stone that the builder rejected, with a vengeance.

In the interior of the continent this skyward urban growth may present no especial advantage other than to raise each aspiring center of population a little farther each century above the monotonous dead level of the surrounding plain. But in the coastal areas the silent, constant accretion may be the salvation of many a metropolis from the predicted 80-foot rise of the oceans as the polar ice caps slowly melt away.

ROUND HOLES FOR ROUND PEGS

A NOTICE in the Massachusetts Medical Society column of this issue of the *Journal* announces the Society's intention of revitalizing its former placement service for physicians. This service, which functioned so capably in the early post-war years under the devoted guidance of Miss Mary Gaston, was discontinued when the peak of its usefulness seemed to be past.

A steady, if small, stream of requests for such advice continues to come into the offices of both the Society and the *Journal*, however, from physicians hunting locations as well as from locations hunting physicians, and it has become apparent that a continuing organized effort should again be made to discharge this needed function.

The happy term "match-making," adopted to characterize the reciprocal search by medical students for hospital appointments and by hospitals for interns, seems to apply to the present considerably simpler situation. It is assumed that cross-matching, as employed in blood laboratories, will not be necessary to ensure compatibility.

The number of idiots supported by Massachusetts, is 20; number of insane, 67; and the number of paupers, made so by intemperance, also housed, fed and clothed by the Commonwealth, exclusive of town paupers, 87.

Boston M. & S. J. *February 8, 1854*

MASSACHUSETTS MEDICAL SOCIETY

PLACEMENT SERVICE

In co-operation with the American Medical Association the Massachusetts Medical Society has set up a Placement Service, for physicians.

Under the direction of Robert St. B. Boyd, executive secretary, attempts will be made to match requests from physicians for locations in Massachusetts with requests from locations for physicians. At present requests from physicians for locations in Massachusetts and New England far outnumber the requests for physicians.

Readers knowing of communities or medical groups looking for physicians can help immeasurably in the match-making process by writing to Mr. Boyd at 22 Fenway, Boston, Massachusetts.

NOTICES

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on February 16 at noon. Dr. Ethan A. Brown, chief of Allergy Section, Boston Dispensary, and staff member, New England Medical Center, will speak on the topic "The Field of Allergy." All physicians are invited.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The winter meeting of the Massachusetts Medico-Legal Society will be held in the George Burgess Magrath Library, Building E 1, Harvard Medical School, on February 17, at 2:30 p.m. The program will include the business meeting and a symposium on fatal and nonfatal rape.

NEW ENGLAND CENTER HOSPITAL HOUSE OFFICERS' ASSOCIATION

A meeting of the New England Center Hospital House Officers' Association will be held in the Stearns Auditorium, New England Center Hospital, on Friday, February 19, at 7 p.m. Thomas P. Almy, New York Hospital, will speak on the topic "Experimental Evidence on the Nature of Cardiospasm." Drs. Franz J. Ingelfinger and Malcolm Stanley will lead the discussion. All interested persons are invited.

HAMPDEN DISTRICT MEDICAL SOCIETY

A meeting of the Hampden District Medical Society will be held at the Massachusetts Mutual Life Insurance Company, Springfield, on Tuesday, February 23, at 6:30 p.m. Officers of the company will speak on the topic "Doctors and the Insurance Companies."

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 5–25. Consultation Clinics for Crippled Children. Page 180.

FEBRUARY 8. New England Cardiovascular Society. Page 129, issue of January 21.

FEBRUARY 9. New York Society for Circulatory Diseases. Page 129, issue of January 21.

FEBRUARY 9. Harvard Medical Society. Page 129, issue of January 21.

FEBRUARY 15, MARCH 1 and 15, APRIL 5 and 19. Hartford Medical Society, Page 1130, issue of December 31.

FEBRUARY 15–20. Pan-American Academy of General Practice. Page 790, issue of November 5.

FEBRUARY 16. Tufts Medical Alumni Lecture. Page 181, issue of January 28.

FEBRUARY 16. South End Medical Club. Notice above.

FEBRUARY 17. Massachusetts Medico-Legal Society. Notice above.

FEBRUARY 19. New England Center Hospital House Officers' Association. Notice above.

FEBRUARY 19–MAY 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

FEBRUARY 20 and 21. Mid-Winter Radiological Conference. Page 130, issue of January 21.

FEBRUARY 23–25. College of Medical Evangelists Alumni Postgraduate Convention. Page 1044, issue of December 17.

FEBRUARY 23. Hampden District Medical Society. Notice above.

FEBRUARY 26 and 27. New England Diabetes Association. Page 129, issue of January 21.

MARCH 3 and APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

MARCH 11–13. American Orthopsychiatric Association. Page 129, issue of January 21.

MARCH 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

MARCH 22–25. American Academy of General Practice. Page 129, issue of January 21.

MARCH 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

APRIL 8–11. International Academy of Proctology. Page 130, issue of January 21.

APRIL 9. New England Society of Anesthesiologists. Page 87, issue of January 14.

APRIL 29, 30 and MAY 1. American Goiter Association. Somerset Hotel, Boston.

MAY 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

MAY 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JULY 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 12. 113th Annual Meeting. Andover Country Club, Andover.

HAMPDEN

FEBRUARY 23. Massachusetts Mutual Life Insurance Company, Springfield.

MIDDLESEX EAST

MARCH 24.

MAY 11. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 11

THURSDAY, FEBRUARY 11

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, FEBRUARY 12

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, FEBRUARY 13

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Auditorium, New England Center Hospital.

(Notices concluded on page xxv)